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Automatic Doppler Signal Analysis to Assess Utero-Placental Circulation for Identifying High Risk Pregnancies

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Abstract— **High risk pregnancy conditions such as pre-eclampsia, pregnancy induced hypertension, intra-uterine growth restriction and gestational diabetes are associated with defective utero-placental circulation. These conditions, if undetected early during pregnancy, are associated with poor pregnancy outcomes including high morbidity/mortality for the fetus/mother. The current state of the art for monitoring such conditions is via (color) Doppler ultrasound with key clinical parameters being observed in uterine and umbilical arteries being the resistance index (RI), pulsatility index (PI) and AB index and early diastolic notching. High risk conditions in pregnancy manifest as abnormal flow profiles and indices in select fetal/maternal blood vessels. These parameters are gold standard as far as current clinical practice goes but they still suffer from low sensitivity in detecting and predicting the above mentioned high risk conditions at an earlier stage. In this paper, we propose a method based on Doppler signal analysis that automatically identifies the above conditions with higher sensitivity even when the current RI/PI indices are normal.**

I. Introduction

A high risk pregnancy is one in which some condition puts the mother, the developing fetus, or both, at higher-than-normal risk for complications during or after the pregnancy and birth [1]. A number of conditions during pregnancy like Hypertensive disorders (Pre-eclampsia), Intra-Uterine Growth Restriction (IUGR) of fetus and gestational diabetes mellitus etc, increases such risks and makes the pregnancy, a high risk one. In developing countries, hypertensive disorders are the second most common obstetrical cause of stillbirths and early neonatal deaths, accounting for 23.6% after spontaneous pre-term delivery (28.7%) [2]. Pre-eclampsia is estimated to be responsible for approximately 14% of maternal deaths per year worldwide (50,000-75,000) in 2004 [3]. Similarly, IUGR of fetuses has a global prevalence of 10% for all pregnancies, with rates of 3-5% for healthy mothers and 25% or higher for some high-risk groups, such as hypertensive mothers. Assessing and monitoring of pregnancies at risk thus, is important to allow for adequate measures to be taken in order to improve maternal and fetal outcomes of a pregnancy and reducing infant and maternal mortality and morbidity.

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Risk assessment is part of routine prenatal care. Various modalities are available to estimate risk in pregnancies. Ultrasound Doppler velocimetry of fetal and maternal blood vessels. Placental pathology has been recognized as an important mechanism behind poor pregnancy outcome in high risk pregnancies. With the availability of Doppler ultrasound, it has been possible to study the placental circulation patterns and their pathologies non-invasively. Ultrasound Doppler based flow velocity waveforms are obtained from maternal (uterine) and fetal (most commonly umbilical and middle cerebral) arteries and analyzed to identify features that can differentiate normal and high risk pregnancies. This procedure has been reported in numerous studies to be a promising technique for predicting the level of risk for conditions like pre-eclampsia and intrauterine growth restriction. Papageorghiou and others [4] observed that Doppler diagnosis of impeded uterine artery flow appropriately identified ~40% of women who subsequently developed pre-eclampsia (6-fold increased risk with positive Doppler) and ~20% of fetal growth restriction cases (3.5-fold increased risk). A number of reviews conclude that the impact of Doppler velocimetry (S/D, RI, PI, uterine notch) on the outcome of a pregnancy at risk could be more significant if combined with additional indicators of fetal compromise [5].

II. Physiology

A. Placental Hemodynamics during Pregnancy

Each uterine artery (on each side of the uterus) originates from internal iliac (hypogastric) artery and reaches the uterus just above the cervix. The main uterine artery branches into arcuate arteries, which arch anteriorly and posteriorly and extend inward for about 1/3rd thickness of the myometrium. They are tortuous and vary in thickness and in the area they supply. The radial arteries arise from the arcuate arteries almost perpendicularly and enter the endometrium of the uterus as the spiral arteries.

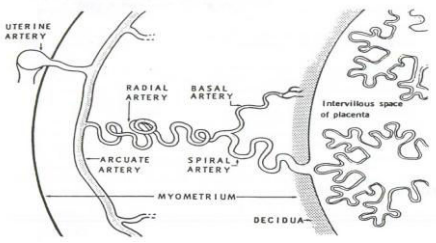


Figure 1: Uterine artery and its branches

A lack of endovascular infiltration by trophoblasts into the myometrial portion of the placental bed spiral arteries is a consistent finding in the presence of preeclampsia and

IUGR [5]. The second wave of endovascular trophoblastic invasion that proceeds in myometrial segments of the spiral arteries from about 15 weeks does not occur in patients who will develop fetal growth restriction or pre-eclampsia. These physiologically un-converted vessels result in increased resistance to the uterine artery blood flow in these cases, compromising the vascular supply to the placenta and hence placing the developing fetus at risk for developing IUGR and the mother for PIH and/or gestational diabetes [5]. Thus, the physiology of the utero-placental circulation in normal pregnancy and at-risk pregnancy complicated by pathology in placental circulation manifesting as pre-eclampsia, IUGR and gestational diabetes mellitus can be summarized as follows:

1. Utero-placental circulation during normal pregnancy is one with progressively reducing downstream impedance and a progressively increasing blood flow volume as the pregnancy progresses which peaks by the end of the second trimester (24 weeks) and remains constant thereafter in the third trimester.

2. Utero-placental circulation in at-risk pregnancies is one with increased impedance downstream and decreased amount of blood flow volume blood flow in the uterine artery which develops during the second trimester and may persist beyond the 24 weeks of gestational age.

B. *Objectives*

Despite the widespread use of Doppler uterine artery monitoring in pregnancy, there is a lack of substantial evidence on the use of Doppler uterine artery monitoring for high risk pregnancy. The Doppler indices do not provide direct information about the amount of blood in the uterine arteries during a pulse cycle, which is a significant factor in the fetal development. The lack of evidence in the performance of the Doppler indices, the timing of examination and quantification of the uterine artery blood flow during the development of the utero-placental circulation present an area of research where additional information can be obtained from the Doppler uterine artery waveform to identify abnormalities in the utero-placental circulation before 24 weeks of gestational age. With this background, the following objectives were set for the study:

1. To study features from the Doppler uterine artery MFE (Maximum Frequency Envelope) that indicate the amount of blood in the uterine artery during a pulse cycle.

2. To study if these features in high risk pregnant women with PIH, GDM and/or IUGR with normal uterine artery Doppler indices are different from women with normal pregnancy with normal uterine artery flow, before 24 weeks of gestation.

III. HYPOTHESIS

Defective trophoblastic invasion of the spiral arteries is significant in the pathogenesis of gestational diseases like pre-eclampsia, IUGR and gestational diabetes mellitus. Decreased downstream resistance in the utero-placental circulation in a normal pregnancy results in an increase in the blood flow velocity and blood volume in the uterine artery. The utero-placental circulation is a system of forward blood flow in the uterine artery even during the diastole of the pulse cycle to ensure continuous blood supply to the placenta during diastole [5]. Thus, the total amount of blood in the uterine artery during a pulse cycle has a systolic component and a diastolic component. With increased impedance, the uterine artery blood volume during a pulse cycle is decreased, as compared to that in a normal pregnancy.

It is hypothesized that the relation between the diastolic and the systolic components of the uterine artery Doppler flow waveform will vary according to the patho-physiology of the utero-placental circulation in normal and at-risk pregnancies. This study compares this relation in normal and at-risk pregnancies with normal Doppler uterine artery flow indices.

A. *Equations: Area under the Max Frequency Envelope Curve (AUC) as a measure of the blood volume*

The anatomical course of the blood from the maternal abdominal aorta to the uterine artery through the Common iliac artery and the internal iliac artery is shown as below:

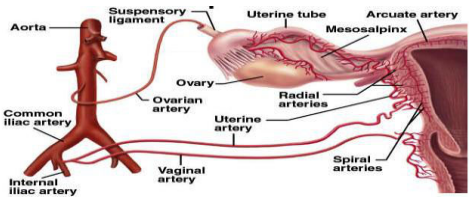


Figure 2: Uterine artery blood flow (Ref: http://on-line.ucol.ac.nz)

In the absence of major structural cardio-vascular and gynecological diseases, the amount of blood in the uterine artery (QUt) can be considered to be a constant fraction of the cardiac output (QA) over a physiological range, i.e.

$$Q_{Ut} = kQ_A \ (k<1)$$

The cardiac output, QA = Heart Rate (H) X Stroke Volume (VA) Thus, $Q_{Ut} = kHV_A$

Since the heart rate is same for the aorta and the uterine artery, it may be assumed that the amount of blood in the uterine artery during each cardiac cycle is proportional to that in the aorta and hence, the AUC of the MFE for the uterine artery can indicate the amount of blood in the uterine artery. The relation between the frequency waveform and the uterine artery volume can also be studied as follows:

Cross-sectional area of the vessel =A
Flow velocity = v
Frequency shift=μ
Magnitude of frequency shift= i
Magnitude of frequency shift α A => $i=k_1A$ (1)
Frequency shift α Velocity => $\mu=k_2v$ (2)
From (1) and (2) we have,

$i\mu = (k_1 k_2)Av$ and therefore

$\int i\mu(dt) = k\int Av(dt)$ .....$k= k_1 k_2$ (3)

Thus area under the frequency curve corresponds to flow volume

B. Assumptions for hypothesis:

1. No loss/leakage of blood from the aorta to the uterine artery to outside the vascular tree.

2. The cross-sectional area of the uterine artery is constant during a pulse cycle.

3. No maternal cardiac arrhythmia and other cardio-vascular diseases or drugs that would result in different pulse rates in different regions of the body (e.g. heart blocks etc.)

4. The position of the mother during the time period of recording the Doppler signals is constant. This would eliminate the action of pelvic muscles to the blood flow along the uterine artery pathway.

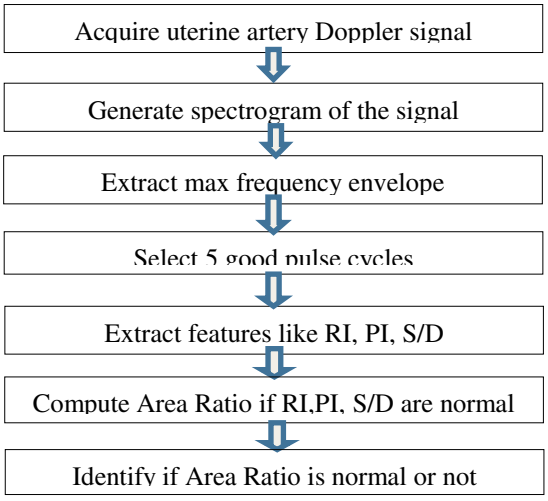
5. No structural uterine anomalies that would lead to a tortuous course of the uterine artery before its division into cervical and corporal branches.

IV. METHODS

The first step of the approach is to acquire ultrasound Doppler uterine artery signals from women with normal and at-risk pregnancy using a color Doppler ultrasound systems or Doppler velocimetry devices. This is followed by developing an algorithm for the extraction of features from the Doppler flow waveform MFE (Area Ratio) and compare them between normal and at-risk pregnancies. The block diagram of the approach is given below.

A. Preprocessing

In this step, spectrogram of the Doppler signal is computed using short term Fourier transform with a 21 millisecond Hamming window with N = 256 data points and 50% overlap. The spectrogram is thresholded to obtain a binary image using mean and IIR filters [6]. The maximum frequency envelope is extracted from the smoothed spectrogram image. This envelope is used for selecting five good pulse cycles.



Block diagram for identifying area ratio automatically

B. Five good cycle selection

Good cycles are critical for robust algorithm development, because ideally features should not capture the signatures from noise and should only represent the blood flow pattern in an artery. The algorithm for detecting peaks in the maximum frequency envelope is based on thresholding the height and depth of the envelope. A point is said to be the peak, if there are lower points around it. A point in the maximum frequency envelope is considered maximum peak if it has the maximal value, and is preceded (to the left) by a value lower by DELTA. DELTA has been empirically determined to be 10. It is assumed that the good cycles should follow the rules as mentioned below:

- Only one peak and valley in each cycle
- Length of the cycle
- Peak strength of the profile
- Completeness of a cycle.

Based on the rules given above, the algorithm for selecting good cycles is as follows:

1) First, it is made sure that there is only one peak between two valleys. This is achieved by changing the value of DELTA in determining peaks and valleys. The remaining cycles are checked for their cycle length i.e. distance between two valleys. Typically, the cycle length for uterine artery is 160 time bins. This is attributed to the heart rate of the mother which is around 85-90 beats/ min which could also go as high as 120 beats/ min during abnormal conditions. Therefore, the acceptable cycle length is selected between 78 time bins and 176 time bins.

2) Finally, continuous 5 good cycles are selected from the longest segment of good cycles for feature extraction.

C. Feature Extraction

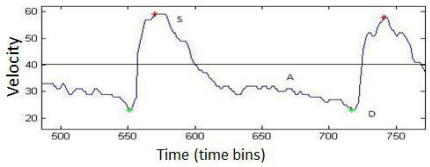


Figure 3: Velocity computation from a pulse cycle

Peak Systolic Velocity (S): The peak for the cycle was taken as the Peak Systolic Velocity

End Diastolic Velocity (D): The valley at the right end of the cycle along the temporal axis was taken as the End Diastolic Velocity.

Average Velocity (A): The average or mean velocity was obtained by summing up all the points on the MFE in one cycle and dividing it by the length of the cycle.

This is followed by exploring the standard indices as follows:

- Resistance index (RI = (S-D)/S) (also called resistive index or Pourcelot's index);
- Systolic/ Diastolic (S/D) ratio, sometimes also referred as the A/B ratio;
- Pulsatility index (PI = (S-D)/A);

The AUC for a pulse cycle is divided into two parts:

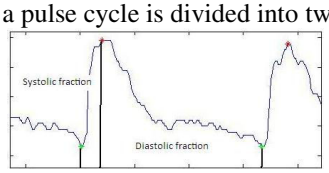


Figure 4: Area under curve

The part of the AUC from the starting point to the Peak Systolic velocity is the Systolic area. The part of the AUC from the Peak Systolic velocity to the end point (End Diastolic Velocity) is the Diastolic area. To make the feature angle independent, the areas were normalized with the Area for the complete pulse cycle. Thus the proposed features studied from the spectrum were as follows:

1. Diastolic Fraction = $AUC_{Diastole}/AUC_{Total}$
2. Systolic Fraction = $AUC_{Systole}/AUC_{Total}$
3. Area Ratio = Sysfrac/Diasfrac

This Area Ratio feature is studied in normal pregnant women with normal flow and with gestational hypertension, gestational diabetes and IUGR having normal flow to see if any abnormality could be detected.

V. Results and Discussions

14 pregnant women with singleton pregnancies between 23-37 weeks of gestational age were recruited for the study. 7 women had normal current pregnancy history with normal Doppler uterine artery indices while 7 had abnormal current pregnancy history with normal Doppler uterine artery indices. Inclusion criteria for **normal population** includes normal singleton pregnancy, normal uterine artery PI and RI for the gestational age at the time of examination, maternal blood pressure within the normal range for the gestational age, no present and past history of any chronic maternal illness, normal obstetric history which included absence of gestational diabetes mellitus, preeclampsia, IUGR or congenital fetal malformations. Inclusion criteria for **abnormal population** include current pregnancy history of pre-eclampsia (3), IUGR (2) and gestational diabetes mellitus (2) with **normal** RI, PI and SDR and absence of early diastolic notch. The standard criteria for clinical classification as PIH, IUGR and gestational diabetes are followed to label a pregnancy as abnormal. Doppler indices are considered normal if they lay between the 5th and the 95th percentile for the values for the gestational age. Both the groups were compared for maternal age and gestational age and were observed to be comparable as shown in table 1.

Comparability of the two groups			
Characteristic	**Normal Group (Mean ±SD)**	**Abnormal Group 2 (Mean ±SD)**	**p Value (<0.05 Significant difference)**
Maternal Age (Years)	**27.71** (±2.75)	**25.14** (±3.36)	**0.16**
Gestational Age (Weeks)	**30.14** (±6.41)	**33.14** (±4.02)	**0.32**

Table 1: This shows that the two groups are comparable

Figure 5 indicates that RI, PI and the S/D ratio values are normal are normal for these patients and are highly correlated [6] and when used together are unable to distinguish normal pregnancies with abnormal. Table 2 shows that the Area Ratio is significantly different between normal and high-risk pregnancies that are not classified by the standard indices (student's t-test). A threshold value of the Area Ratio at 0.6 was observed to have the highest sensitivity and specificity as shown in the confusion matrix. Thus, Table 3 shows that area ratio, thresholded at a value of 0.6, classified high risk and normal pregnancies with sensitivity of 86% and specificity of 100% between the two groups that were not differentiated by the standard indices.

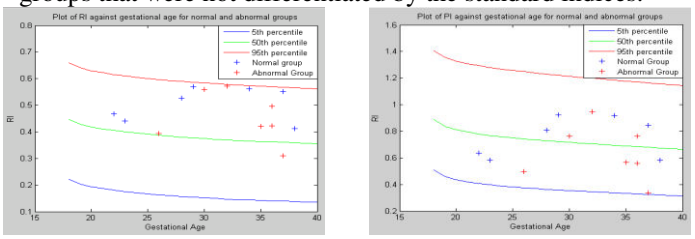


Figure 5: Plot for RI and PI values against GA show that the values are normal

Feature	**Normal Group Mean (±SD)**	**Abnormal Group Mean(±SD)**	**p Value (<0.05 significant)**
RI	0.51 (±0.07)	0.45 (±0.09)	0.25
PI	0.76 (±0.15)	0.63 (±0.20)	0.22
S/D Ratio	2.07 (±0.27)	1.87 (±0.31)	0.20
Area Ratio	0.38 (±0.15)	0.91 (±0.31)	**0.003**

Table 2: Comparison of Area Ratio with standard clinical indices

Confusion Matrix for area ratio at a threshold value of 0.60		
Signal	True high risk (7)	True normal (7)
Classified as High risk	6	0
Classified as normal	1	7

Table 3: Confusion matrix for Area Ratio

VI. Conclusion

It is observed that the placental pathology is associated with majority of pregnancies complicated by hypertensive disorders, IUGR and diabetes mellitus etc. Abnormal utero-placental circulation in high-risk pregnancies includes abnormalities in uterine blood flow velocity as well as the uterine blood volume during a pulse cycle (stroke volume). The "Area Ratio" can be used in classifying high-risk pregnancies with normal uterine artery flow velocity based indices. Identifying changes in the quantity of the blood supply to the fetus can improve the performance of the Doppler uterine artery investigation in high-risk pregnancies having normal velocity based indices. However this study needs to be validated with larger sample size.

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