Ultrasound in Med. & Biol., Vol. 33, No. 7, pp. 1057–1063, 2007

0301-5629/07/$–see front matter

doi:10.1016/j.ultrasmedbio.2007.01.012

● *Original Contribution*

APPLICATION OF THE MAGNITUDE-SQUARED COHERENCE FUNCTION BETWEEN UTERINE AND UMBILICAL FLOW VELOCITY WAVEFORMS FOR PREDICTING PLACENTAL DYSFUNCTION: A PRELIMINARY STUDY

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(*Received* 27 *October* 2006; *in final form* 25 *January* 2007)

Abstract—To examine whether the magnitude-squared coherence between uterine and umbilical blood flow velocity waveforms can, in conjunction with estimated fetal weight, uterine and umbilical pulsatility indices, fetal and maternal heart rates, diastolic notching and the amniotic fluid index, create a sensitive and specific model for the prediction of placental dysfunction. Binary logistic prediction models are created for preeclampsia, pregnancy induced hypertension and intrauterine growth restriction in a study group of 284 unselected midtrimester pregnancies. In each study group, the median value of derived parameters were compared with the uncomplicated pregnancy control group. The magnitude-squared coherence function between the uterine and umbilical flow velocity waveforms was found to be a statistically significant predictor of preeclampsia during the midtrimester of pregnancy. The magnitude-squared coherence did not improve the prediction of intrauterine growth restriction or pregnancy induced hypertension. The inclusion of magnitude-squared coherence as one of the prediction parameters may improve the early identification of pregnancies subsequently complicated by preeclampsia. (E-mail: p.struijk@erasmusmc.nl) © 2007 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Fetus, Preeclampsia, Pregnancy induced hypertension, Intrauterine growth restriction.**

INTRODUCTION

Preeclampsia (PE), pregnancy induced hypertension (PIH) and intrauterine growth restriction (IUGR) are common pregnancy complications that are associated with placental dysfunction and increased perinatal morbidity and mortality (Villar et al. 2006). Evidence exists linking these conditions to suboptimum placental development early in pregnancy, long before the pregnancy complications are clinically manifested (Baschat and Hecher 2004). As a result, it should be possible to detect altered placental function before the onset of symptoms. This capability would allow for appropriate antenatal management of at-risk pregnancies as well as identification of pregnancies at low risk for complications. Over the last decade, a number of studies have demonstrated that pregnancies with abnormal uterine (Baschat and Hecher 2004; Campbell et al. 1983; Papageorghiou et al. 2004; Yu et al. 2005) or umbilical (Baschat and Hecher 2004; Fong et al. 1999; Spinillo et al. 2004) artery Doppler velocimetry are at higher risk for adverse fetal outcome. Despite the advancement in ultrasound technology, there is not a test available that is highly sensitive and specific to predict adverse fetal outcome in pregnancy.

Doppler flow studies have demonstrated that umbilical artery blood flow velocity waveforms interact with environmental pressure changes. When women move from either the standing or the lateral position to the supine position, the umbilical pulsatility index rapidly

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increases, which indicates rise in vascular resistance (Marx et al. 1986; van Katwijk and Wladimiroff 1991). One possible explanation for this phenomenon is the compression of the terminal villi during such movements (Karimu and Burton 1994).

In a previous study, we showed that even though fetal heart beat variability is almost absent before the 15th week of gestation, power spectral analysis showed similar variations between umbilical and uterine flow velocity variabilities. Such similarities included a peak at the maternal respiration frequency in both spectra (Struijk et al. 2001). This study suggested that intervillous pressure fluctuations might induce umbilical flow velocity variability. The dynamic placenta model described by Talbert and Sebire supports this theory (Talbert and Sebire 2004; Talbert 1995). The barrier between maternal and fetal blood, the so-called vasculo-syncytial membranes of the human placental terminal villi, is very permeable to water (Sibley and Boyd 1992). The high permeability of this membrane to water implies that the time average pressure on each side of the membrane should be in equilibrium to prevent excessive water transport from the fetus to the mother or, with a reverse pressure gradient, water entry from the mother to the fetus (Talbert and Sebire 2004). This so-called transmural pressure is dynamic and there is continual fluctuation because of pulsatility in the fetal and maternal circulations (Sebire and Talbert 2004). The membrane of the terminal villi will move inwards with compression and move outwards with relaxation, increasing and decreasing the intravillous volume and resistance to flow in a complex rhythm determined by both the fetal and maternal heart beat frequency. As a consequence, a frequency component at the maternal heart rate should be present in the umbilical blood flow velocity waveform. Similarly, a frequency component at the fetal heart rate should be present in the uterine velocity waveform.

In summary, there is a critical balance between intra- and intervillous pressures. We hypothesize that any disturbance of this balance might be reflected by altered uterine and umbilical flow velocity interaction and indicate placental dysfunction.

The magnitude-squared coherence function (Kay 1988) is a measure of the correlation between two signals in the frequency domain. In this paper, we evaluate the magnitude-squared coherence between blood flow velocity waveforms in the uterine and umbilical arteries at the maternal and the fetal heart rate to describe the interaction between maternal and fetal blood flow waveforms. The objective of the study is to examine whether the magnitude-squared coherence function at the fetal and maternal heart rate could, in conjunction with estimated fetal weight, uterine and umbilical pulsatility indices, fetal and maternal heart rates, diastolic notching and the amniotic fluid index, create a sensitive and specific model for the prediction of placental dysfunction.

MATERIALS AND METHODS

Subjects

Between October 2003 and September 2004, pregnant women visiting the Maternal-Fetal Medicine Outpatient Clinic of the McKay-Dee Hospital in Ogden (Utah, USA) for a midtrimester ultrasound examination were asked to participate in this study. The hospital ethics committee approved the study and written informed consent was obtained from each of the 299 women agreeing to participate in the study. Nine women were lost to follow-up and six women were excluded because of incomplete data sets.

A woman was classified as belonging to a control subset if her pregnancy was uncomplicated and she delivered a healthy child at more than 36 weeks of gestation whose birth weight was within the 5th and 95th percentile reference lines of the Hadlock weight standard (Hadlock et al. 1991). A patient with diastolic blood pressures greater than 90 mmHg on two different occasions during pregnancy, but with no proteinuria, was diagnosed as belonging to the pregnancy induced hypertension (PIH) group. PE was diagnosed if hypertension occurred with an episode of significant proteinuria, defined as more than 300 mg protein in a 24-h urine collection or at least 2+ protein by dipstick. Finally, the IUGR group composed of pregnancies, not belonging to the PIH or PE groups, resulting in children whose birth weights were below the 5th percentile.

Ultrasound recordings

Ultrasound examination was performed with an Acuson Sequoia 512 ultrasound device (Acuson, Inc. Mountain View, CA, USA), using a 6.0 MHz transabdominal transducer. Morphometric measurements on all fetuses included biparietal diameter, head and abdominal circumferences and femur length. The fetal weight was estimated using the Hadlock formula (Hadlock et al. 1985). The estimated fetal weight and birth weight are expressed as z-scores using the Hadlock weight standard (Hadlock et al. 1991). The four-quadrant amniotic fluid index was measured using the technique of Phelan and associates (Phelan et al. 1987).

Doppler flow velocity waveforms from the umbilical artery were obtained from a free-floating loop of the umbilical cord, typically near the placental insertion to minimize movement artifacts. For the uterine artery velocity waveforms, the transducer was placed in the lower lateral quadrant of the uterus on the placental side and angled medially until the crossover of the main uterine artery and the external iliac artery and vein could be identified. This crossover was used as a reference point to identify the main uterine artery. In 2D color Doppler mode, the sample volume was placed on the spot where the highest color Doppler velocity was seen for both the umbilical and uterine artery to ensure that the insonation angle was as close as possible to zero degrees. The forward and backward Doppler audio signals, digitized at 12 kHz, were transferred to an external computer for off-line analysis. Umbilical and uterine artery flow velocity recordings of approximately 30-s duration were obtained in sequence with a time interval between the Doppler recordings of the two vessels of less than 5 min.

Off-line analysis

The blood flow velocity waveform was reconstructed from the audio signals using the modified geometric method for maximum frequency estimation (Fernando et al. 2004a). The pulsatility index was defined as the maximum velocity minus the end diastolic velocity divided by the time averaged velocity. The mean value of all heartbeats during the registration period was calculated and used for further analysis. The maternal and fetal heart rates were derived from the first peak of the autocorrelation function of the velocity waveforms. The coherence function measures the similarity between two signals in the frequency domain. Let $x(n)$ and $y(n)$ represent the uterine and umbilical artery flow velocity waveforms. The magnitude-squared coherence between the two signals is defined as

$$C_{xy}(f) = \frac{|S_{xy}(f)|^2}{S_{xx}(f)S_{yy}(f)}$$

where S_{xy} is the cross spectral density of the two waveforms, S_{xx} and S_{yy} are the power spectral densities of the individual waveforms and f is the frequency variable. The magnitude-squared coherence function takes values between zero and one and is calculated at the maternal and the fetal heart rates in this work (Fernando et al. 2004b). The magnitude-squared coherence analysis is independent of phase differences and delays between two signals. Consequently, this function will remain the same for sequentially and simultaneously collected maternal and fetal blood flow velocity waveforms as long as the relationships among the signals do not change during the data collection interval. Signal stability is assumed during the time interval of less than 5 min between the Doppler recordings. We use sequentially collected data because simultaneous collection resulted in data with significant signal interference. MATLAB software version 6.5 release 13 (Mathworks Inc., Natick, MA, USA) for Windows 2000 professional was used to perform all the calculations on a Pentium *4* computer.

Statistical analysis

The variables used in the analysis are summarized by the median and interquartile range (IQR) and comparisons between groups were made using the Mann-Whitney *U* test. Statistical significance was defined as a p value < 0.05. In the study group of 284 pregnant women, the risk of IUGR as reflected by small for gestational age delivery, PIH and PE was modeled using binary logistic regression. Statistically significant effects and interactions were identified by backward stepwise elimination using the likelihood ratio test. The probability criterion for stepwise entry was set to 0.05 and for removal from the equation, to 0.1. All statistical analysis were performed using the SPSS statistical package (SPSS Inc, Chicago, IL, USA) version 11.1.

RESULTS

The characteristics of the 284 subjects of this study and their pregnancy outcomes are summarized in Table 1. The median values and the interquartile range of the body mass index of the mothers when presented for delivery were available from 49,480 Utah birth records in the year 2003. Comparison of the values associated with our study with data from this large sample indicates that the body mass indices of the study group are representative for Utah residents.

A total of 18 children were born small for gestational age, two in the PE group and two in the PIH group

Table 1. Patient characteristics and fetal outcome

Age at birth (years)	Median (IQR)	27 (24, 31)
Height (cm)	Median (IQR)	165 (160, 170)
BMI at birth	Median (IQR)	29 (26, 33)
Gestational age at exam (wk)	Median (IQR)	19.7 (18.9, 20.4)
Notching	N (%)	
Diastolic notch		37 (13)
No notch		247 (87)
Parity	N (%)	
Nulliparous		101 (35.6)
Multiparous		183 (64.4)
Pregnancy complications	N (%)	
Preeclampsia		8 (2.8)
Pregnancy induced hypertension		9 (3.2)
Type I diabetes mellitus		1 (0.4)
Gestational diabetes		6 (2.1)
Proteinuria		4 (1.4)
Chronic hypertension		3 (1.1)
Rh-D isoimmunization		1 (0.4)
Beta-Haemolytic streptococcus		4 (1.4)
Chlamydia		1 (0.4)
Intra uterine fetal death		2 (0.7)
Pregnancy outcome		
Gest. age at delivery (wks)	Median (IQR)	39.0 (38.1, 39.4)
Gest. age <36 wk	N (%)	15 (5.3)
Birth weight (grams)	Median (IQR)	3312 (3014, 3573)
Birth weight $<P_5$	N (%)	18 (6.3)
Birth weight $>P_{95}$	N (%)	8 (3.2)

Table 2. Characteristics of the control and study groups

	Control group	IUGR	PIH	PE
GA at examination (wk)	19.7	20.1	18.9	19.0
Median (IQR)	(18.9, 20.4)	(19.0, 21.0)	(18, 19.7)	(17.9, 19.9)
GA at birth (wk)	39.0	39.2	39	37.7
Median (IQR)	(38.4, 39.6)	(38.3, 39.4)	(37.6, 39.4)	(36.2, 39.3)
Maternal age (year)	27	26	23	27
Median (IQR)	(24, 31)	(22, 30)	(21, 33)	(23, 34)
Nulliparous – N (%)	78 (36)	6 (43)	4 (44)	4 (50)
Diastolic notching – N (%)	22 (10)	4 (29)	3 (33)	3 (38)
Z-score est. weight at exam	0.20	−0.51*	0.40	−0.12
Median (IQR)	(−0.34, 0.69)	(−1.64, 0.44)	(−0.35, 1.15)	(−0.99, 0.85)
Amniotic fluid index (cm)	13.7	14.9	12.8*	11.7*
Median (IQR)	(12.3, 15.2)	(12.8, 17.0)	(10.8, 13.4)	(10.7, 13.0)
Fetal HR (bpm)	148	149	150	145
Median (IQR)	(143, 153)	(145, 155)	(145, 152)	(141, 154)
PI umbilical art.	1.30	1.10	1.43	1.42
Median (IQR)	(1.18, 1.42)	(0.99, 1.21)	(1.20, 1.55)	(1.01, 1.64)
Maternal HR (bpm)	80	83	91*	81
Median (IQR)	(75, 89)	(77, 85)	(84, 99)	(74, 94)
PI uterine artery	0.80	0.68	0.82	0.85
Median (IQR)	(0.64, 1.08)	(0.48, 0.93)	(0.68, 1.21)	(0.62, 1.31)
Coherence at MHR (%)	33	22	38	19*
Median (IQR)	(21, 48)	(16, 33)	(21, 68)	(10, 27)
Coherence at FHR (%)	27	17	21	24
Median (IQR)	(14, 49)	(11, 46)	(7, 29)	(14, 33)

IUGR (intra uterine growth restriction), PIH (pregnancy induced hypertension) and PE (preeclampsia) groups are compared with the control group.
* $P < 0.05$ according to the Mann Whitney U test.

and the remaining children with birth weight <5th percentile were born in the IUGR group. The *z*-score for birth weight in the IUGR group ($n = 14$) ranged from −2.96 to −1.65.

Two hundred sixteen women at gestational age more than 36 wk gave birth to a healthy child with birth weight within the 5th and 95th percentile reference lines. This formed the control group for this study. The median value of the birth weight expressed as its *z*-score is −0.2 (IQR = −0.7, 0.4) in the control group. In the preeclamptic group ($n = 8$), the median *z*-score is −1.1 (IRQ = −2.2, 0.1). The significantly lower *z*-score for the preeclamptic children indicates that they are born smaller for gestational age than children born in the control group. The *z*-score for birth weight in the PIH group ($n = 9$), −0.68 (IQR = −1.6, −0.08) is statistically not different from that of the control group.

The median and the IQR as well as the frequency of nulliparity and uterine artery diastolic notching in the study groups are compared with those of the control group in Table 2. Already at examination, the median *z*-score of the estimated fetal weight was significantly lower in the IUGR group than that of the control group. In the PIH group, the amniotic fluid index was significantly lower statistically while the maternal heart rate was significantly higher than that of the control group. The amniotic fluid index and the coherence at the maternal heart rate were both significantly lower in the preeclamptic group.

The prediction results and variables selected in the binary logistic models are summarized in Table 3. In the

Table 3. Binary logistic regression results

	Variables selected□	Threshold (%)•	Sensitivity (%)	Specificity (%)	Odds ratio	95% confidence interval	
IUGR	Z-score est. weight	6.5	71	78	0.423	0.229	0.780
	Amniotic Fluid				1.232	1.011	1.502
PIH	Maternal HR	3.5	78	73	1.071	1.008	1.137
	Diastolic notch				3.654	0.847	15.77
PE	Coherence MHR	5	75	72	0.921	0.861	0.986
	Diastolic notch				5.219	1.107	24.61

IUGR: intra uterine growth restriction; PIH: pregnancy induced hypertension; PE: preeclampsia.
□ Variables selected in the binary logistic model.
• Women were considered screened positive if the probability was above this predicted risk level.

group of 284 subjects, the fetal heart rate, the uterine and umbilical artery pulsatility indices and the coherence at the fetal heart rate did not reach statistical significance in the binary logistic prediction models for IUGR, PIH and PE.

The *z*-score for estimated fetal weight and the amniotic fluid index at midpregnancy are predictive factors for IUGR. As could be expected, pregnancies with low *z*-scores for estimated weight at midpregnancy are at higher risk to give birth to small for gestational age children; the risk is even more if the amniotic fluid index is high at midgestation.

Increased maternal heart rate and the existence of diastolic notching in the uterine artery waveform are risk factors for PIH. In spite of the statistically significant lower median value for amniotic fluid index in women with PIH when compared with normal controls, this variable could not contribute to a better prediction in conjunction with maternal heart rate and diastolic notching in the binary logistic model. The odds ratio for maternal heart rate seems to be small but it should be considered that heart rate is expressed in beats per min. To calculate the odds ratio for a pregnant woman whose heart rate is 10 beats per min above average, the odds ratio of 1.071 should be raised to the power of 10, which is about 2.

The risk factors found for PE are the magnitude-squared coherence at the maternal heart rate and diastolic notching. As with the prediction of PIH, the relative low amniotic fluid index could not contribute to a better risk prediction for PE. On a zero to one scale for the magnitude-squared coherence, the odds ratio is smaller than a thousandth. To avoid these small numbers, we have chosen a zero to hundred-percentage scale for the magnitude-squared coherence values.

The odds ratio is an estimate for relative risk. To calculate the relative risk to develop PE for a woman whose magnitude-squared coherence at the maternal heart rate is 10% below average, the odds ratio of 0.921 should be raised to the power of −10, which is 2.278. If in this example diastolic notching is present in the uterine artery blood flow velocity waveform, the relative risk to develop PIH equals approximately 12, which is the product of the odds ratio for the coherence value (2.278) and the odds ratio for the presence of notching (5.291).

DISCUSSION

The reduction in the median amniotic fluid indices for the PE and the PIH groups was statistically significant when compared with the control group. However, all the values were found to be within the 5th and 95th percentile range (Moore and Cayle 1990). In contrast, the amniotic fluid index was relatively higher in the IUGR group. In this series, a fetus at 20 wk of gestation with a high amniotic fluid index is more at risk for idiopathic IUGR. Since the latter finding may appear counter-intuitive, it must be emphasized that IUGR assorted with known causes (PE 2; PIH 2) is not included in IUGR group. Furthermore, amniotic fluid index in these IUGR pregnancies were measured at midpregnancy. It is not known if oligohydramnios developed later in pregnancy.

Sebire and Talbert have presented an interesting hypothetical model of fetal mechanisms with emphasis on the importance of the fluid balance between the mother and the fetus (Sebire and Talbert 2004; Talbert and Sebire 2004). A cotyledon consists of a number of fetal villous trees with tips anchored in the basal plate surrounding a spiral artery outlet. Blood from the spiral artery will stretch the fetal villous trees outwards, forming a hollow globular shape as a result of the transcotyledonary flow resistance (Talbert 1995). A failure of the spiral arteries to transform from high-resistance arteries to low-resistance pathways during pregnancy might result in low intervillous pressure. The pressure on the other side of the membrane of the terminal villi, the so-called intravillous pressure, would drive water from the fetal circulation to the mother and this may lead to oligohydramnios. It is likely that the fetus attempts to control its fluid volume with a corresponding increase in vasoconstrictive hormone production, which could cross into the maternal circulation. Inadequate remodeling of the spiral arteries and, consequently, poor perfusion of the intervillous space is widely accepted as the primary pathophysiology of PE and to a certain extent for PIH. The reduced amniotic fluid index in these groups likely indicates the inability of the fetus to fully compensate for poor utero-placental perfusion. Based on a large antenatal care trial, it was recently stated that preeclampsia and unexplained intrauterine growth restriction, often assumed to be related to placental insufficiency, seem to be independent biologic entities (Villar et al. 2006). Our finding that increased instead of decreased amniotic fluid index is predictive for unexplained IUGR seems to underline this statement.

In this series, women destined to develop PIH or PE were more likely to have diastolic notching of the uterine artery Doppler waveform. Increased maternal heart rate is observed in the PIH group. Moreover, the logistic regression analysis demonstrates that maternal heart rate contributes significantly to the prediction of hypertension.

Since the magnitude-squared coherence function is a measure of the correlation between two signals in the frequency domain the mean magnitude-coherence value at the maternal heart rate of 19% (0.19) in the PE group can be considered as a lack of coherence. Using a mathematical model of the uteroplacental circulation, Talbert

(1995) demonstrated that increased flow resistance of the spiral arteries did not introduce notching in the uterine flow velocity waveform. Instead, it reduces center cotyledon pressure and the pulsatile part of the pressure waveform is almost absent. This is consistent with the lack of coherence found in the PE group. After all, if maternal pressure pulsations are absent, coherence at the maternal heart rate with the fetal circulation is impossible. In Talbert's mathematical model, it is also demonstrated that notching in the uterine artery flow velocity waveform is associated with increased uterine and arcuate artery compliances and not with increased flow resistance. According to this model, notching reflects uterine and arcuate compliances, while a lack of coherence might reflect high spiral artery resistance. Our finding that both notching and coherence contribute to the prediction of PE is consistent with this theory.

The mean magnitude-squared coherence value at the maternal heart rate of 33% (0.33) between uterine and umbilical flow velocity waveforms found in uncomplicated midpregnancies can be interpreted as a moderate correlation. The pressure waveforms in the centers of human cotyledons are unknown. The moderate coherence in uncomplicated pregnancies and the significant lack of coherence at the maternal heart rate in PE pregnancies along with its predictive value produce evidence for the existence of pulsatile pressure in center cotyledons in uncomplicated human pregnancies. This study provides no evidence for the existence of pulsatile pressure in the capillary villi.

It was demonstrated in a large English study consisting of more than 32,000 pregnant women that the presence of a diastolic notch and the pulsatility index of the uterine artery blood flow velocity waveform were predictive factors for preeclampsia (Yu et al. 2005). We speculate that the sensitivity and specificity of this observation can further be improved if the coherence at the maternal heart rate is included in future studies that target women with risk factors such as a family history of preeclampsia (Esplin et al. 2001; van Dijk et al. 2005), nulliparity, obesity or underlying microvascular diseases.

Although these preliminary results are encouraging, larger studies will be necessary to validate these prediction formulas. Large multicenter studies, such as the English study discussed above (Yu et al. 2005), are needed to develop prediction formulas that can be applied for screening purposes. However, it can be concluded from this study that the inclusion of coherence at the maternal heart beat frequency can significantly improve the prediction of PE.

Nevertheless, it must also be emphasized that a single prediction model is unlikely to identify all pregnancy related diseases. Refinement of this technique for identification of women at low risk for placental dysfunction also deserves further study. The combination of these inexpensive bedside ultrasound measures with more sophisticated, and currently much more expensive, genomics, proteomics and metabolomics analysis also hold great potential, perhaps akin to the integrated maternal serum and ultrasound screens now being utilized for Down Syndrome screening (Malone et al. 2005).

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