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Ultrasound measurement of fetal arterial pulse pressure using phased-tracking methods: A phantom study and clinical experience with antenatal corticosteroid therapy

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Abstract

Aim: This study aimed to compare the accuracy of fetal pulse pressure estimated with a vascular simulator with that obtained by a manometer (reference) and evaluate the pulse pressure in normal human fetuses and fetuses whose mothers received corticosteroids.

Methods: Fetal pulse pressure was estimated as the product of blood flow velocity and pulse wave velocity, based on the water hammer equation. Ultrasonic raw radiofrequency signals for blood flow velocity were captured from the fetal descending aortas at the diaphragm level, and pulse wave velocity was simultaneously measured from different directions using the phased-tracking method. First, the precision and accuracy of pulse pressure in the estimated method were verified by a circulatory phantom simulator, which reproduced fetal blood flow using a pulsating pump. Then, the pulse pressure of 98 normal human fetuses after 17 weeks of gestation and the fetal pulse pressure in 21 mothers who received antenatal corticosteroids for fetal maturation were measured.

Results: A significant correlation between the estimated pulse pressure values and the actual values was found in the phantom simulation ($r = 0.99$, $P < 0.01$). The estimated pulse pressure was significantly correlated with gestational age in normal fetuses ($r = 0.74$, $P < 0.01$). In steroid-treated pregnant women, fetal pulse pressure was observed to increase significantly on the second day of administration ($P < 0.01$).

Conclusion: A noninvasive and accurate estimation model of fetal pulse pressure could be established using phased-tracking method, and this method has the potential to improve the assessment of human fetal hemodynamics.

Key words: fetal pulse pressure, phased-tracking method, pulse wave velocity, vascular simulation model.

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Introduction

Adequate blood flow is necessary to facilitate sufficient oxygen supply to all tissues in humans including fetuses. Obstetricians focus on fetal blood pressure, as pathological fetal hypotension (low blood pressure), rather than hypoxemia, could lead to tissue hypoperfusion, which is a significant causal factor of brain damage in compromised fetuses.[1] However, fetal blood pressure monitoring is rarely a part of the clinical management of fetuses with critical conditions because the standard monitoring methods used in adults is too invasive for fetuses.

With recent advancements in ultrasound technology, noninvasive methods of fetal blood pressure estimation have been sought.[2–6] Several studies have reported a linear relationship between blood pressure and internal diameter or fractional area change in the descending aorta in animal models.[2–4] Although this method gives us meaningful parameters regarding blood pressure changes, it is not intended for the direct determination of the fetal blood pressure. On the other hand, Struijk *et al*.[5] and Miyashita *et al*.[6] reported that fetal pulse pressure could be calculated directly using the change in aortic diameter and pulse wave velocity (PWV) measurement, based on the Windkessel model. However, there is a discrepancy in the results between the two studies regarding fetal pulse pressure values.[5,6] Furthermore, both calculated values were markedly higher than the invasively derived left ventricular pressures in human fetuses that have been previously reported.[7]

The aim of this study was to establish an estimation model of fetal pulse pressure using phased-tracking method based on the water hammer equation, including blood flow velocity and PWV in the fetal descending aorta, in two phases: First, to perform experimental measurements using a vascular simulation model for pressure calibration and to compare the values to those from previously reported estimating equations, such as the water hammer, Bramwell-Hill and Moens-Korteweg models; then, to evaluate the ontogenic change in pulse pressure in normal fetuses and the vasopressor effects of exogenous corticosteroid exposure for lung maturation on fetuses who are at risk of preterm birth to ensure the clinical significance of the current model and to thus provide a novel indicator for fetal hemodynamics.

Methods

Ultrasonic phased-tracking method and PWV measurement

An ultrasonic beam scanned different directions at a frame rate of 500 Hz using an ultrasonic diagnostic equipment (Prosound F75; Hitachi-ALOKA) with a 5-MHz convex array probe (Hitachi-ALOKA). The radiofrequency signals were sampled at 20 MHz for several pulsation cycles. For the *in vivo* measurements, the fetal descending aortas were identified in the longitudinal direction at the diaphragm level in the transabdominal B-mode plane. The radiofrequency signal in each scan line was captured for 2–4 s.

The ultrasonic phased-tracking method was used to estimate the vibration velocities of the phantom and aortic walls. Before applying the phased-tracking method, off-line quadrature demodulation was applied to the sampled radiofrequency signals. The principles underlying phased-tracking method, including the theoretical and *in vivo* evaluation of the measurements, have been previously described.[6] The phased-tracking method was applied to the ultrasonic beams from two different longitudinal positions in the near wall of the descending aorta. A measuring point was set at the upper side of the diaphragm, and another point was set at the lower side. The cross-correlation function between the velocity waveforms at these two positions was obtained to estimate the propagation time delay of the pulse wave between these two positions. To estimate the time delay, which is smaller than the frame interval, reconstructive interpolation was used to interpolate the cross-correlation function.[8] We confirmed that the sampling frequency, which corresponds to the frame rate, was high enough to include all frequency components of the vibration velocity in the phantom or fetal aortic wall based on the Nyquist frequency. The PWV was obtained by dividing the distance between the analyzed positions by the estimated time delay. The average time delay from several cardiac cycles was used for the analysis.

Algorithm to estimate aortic pulse pressure

In the water hammer equation, pulse pressure is calculated as follows:

$$\Delta p = \rho \times U \times PWV \text{ [Pa]} \quad (1)$$

where Δp is the pulse pressure and ρ is the blood's density.[9] This equation assumes that blood density is a constant number (1.05 g/mL) that is not dependent on gestation age and that blood flow velocity is half of the maximum laminar flow velocity, based on the Hagen-Poiseuille law. Thus, fetal pulse pressure was estimated from blood flow velocity and PWV. Blood flow velocity was measured using the same ultrasonography probe at the same level of the descending aorta, the sample volume was assumed to be at the center of the vessel, and the maximum velocity was recorded for an average of five cardiac cycles. The angle of insonification was kept as low as possible (<30°).

Struijk *et al*.[5] and Miyashita *et al*.[6] have reported fetal pulse pressure measurements using the Bramwell-Hill and Moens-Korteweg equations. However, these two equations require the measurement of the aorta's internal diameter change, instead of the blood flow velocity:

$$\Delta p = \rho \frac{D_{\max}^2 - D_{\min}^2}{D_{\min}^2} \times PWV^2\,[\mathrm{Pa}] \quad \text{Bramwell-Hill equation} \tag{2}$$

$$\Delta p = 2\rho \frac{D_{\max} - D_{\min}}{D_{\max}} \times PWV^2\,[\mathrm{Pa}] \quad \text{Moens-Korteweg equation} \tag{3}$$

In these equations, $D_{\min}$ and $D_{\max}$ are the internal vessel diameters during diastole (measured using M-mode) and systole, respectively. The $D_{\max}$-$D_{\min}$ term was measured using the phased-tracking method.

Testing the algorithm using simulation-derived pressure and flow waveforms

Phantom simulation experiments were performed to evaluate the precision and accuracy of the pulse pressure measurements. The phantom consisted of a pulsatile flow generator (TOBI HTJ-1000), a silicone tube in a water tank, a manometer and simulated blood (model 046; Eastek Corporation) (Fig. 1). The pulsatile flow generator could create various pulse pressures by changing the stroke volume from 10 to 50 mL at each stroke. The radiofrequency signals were captured using the same settings used for pulse pressure measurement, and the ultrasonography probe was placed downward in the water tank with the silicone tube.

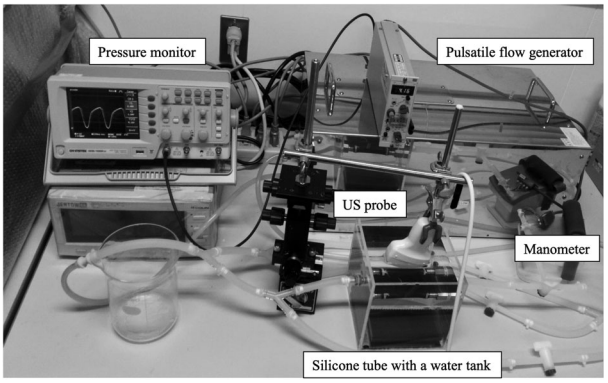

Figure 1 Experimental setup consisting of a pulsatile flow generator, a silicone tube with a water tank, a manometer, an ultrasound (US) probe, a pressure monitor and simulated blood.

Testing the algorithm using clinical data

We prospectively recruited healthy women with singleton pregnancies at our hospital from June 2010 to December 2017. Fetuses with apparent anomalies, such as structural heart disease, arrhythmia, hydrops, chromosomal abnormalities and congenital infection, were excluded. Women with multiple pregnancy or medical complications, such as diabetes, anemia, drug abuse, alcoholic/smoking history, hypertension and significant heart, liver or renal disease, were also excluded.

After applying the exclusion criteria, 119 women with singleton pregnancies (18–40 weeks of gestation) were enrolled. Ninety-eight normal fetuses were observed to examine the normal ontogenic changes. Twenty-one fetuses at 23–33 weeks of gestation were tested to determine the pharmacological effects of exogenous antenatal corticosteroids administered to pregnant women at risk for preterm birth to facilitate fetal lung maturity. A complete course of corticosteroids was defined as two doses of 12 mg intramuscular betamethasone administered 24 h apart. Measurements were performed before the initial administration of betamethasone (day 0) and then on days 2 and 8. The raw ultrasonic radiofrequency signals for blood flow velocity were captured from the fetal descending aortas at the diaphragm level, and PWV was simultaneously measured from different directions. The fetal pulse pressure was calculated from the water hammer equation in clinical data.

This study complies with the policies and/or procedures of the *Journal of Obstetrics and Gynecology Research*. This study was conducted in accordance

with the Declaration of Helsinki and Good Clinical practice. This protocol was approved by the institutional ethics committee, and all measurements were performed with written informed consent.

Statistical analysis

All measured data were analyzed using JMP version 10.0.2 (SAS). Both linear and nonlinear regression analyses were used to build the regression models. One-way analysis of variance and the Tukey–Kramer method were used to compare the pulse pressures at days 0, 2 and 8 from fetuses exposed to antenatal steroids.

Results

Experimental pressure calibration

In the phantom simulation experiment, the PWV increased with increasing pulse pressure in the circuit as the pulsatile pump produced six levels of pressure (ranging from 40–90 mmHg). Figure 2 shows the correlation between the pulse pressure values, as measured using the manometer, and the estimated pulse pressure values from the different estimating equations. The pulse pressure values estimated from the water hammer equation significantly correlated with the pulse pressure measured by the manometer, but there were some conflicts between the two values on the higher or lower pressure range. The estimated pulse pressure values from the Moens-Korteweg and Bramwell-Hill equations were markedly different from the measured values. The equations for the regression line were as follows: water hammer equation: $y = 1.724 \times G\text{-}40.978$ ($r^2 = 0.99$, $P < 0.01$); Moens-Korteweg equation: $y = 3.315 \times G\text{-}134.07$ ($r^2 = 0.79$, $P = 0.054$); Bramwell-Hill equations: $y = 3.161 \times G\text{-}124.26$ ($r^2 = 0.80$, $P < 0.01$), where y is the estimated pulse pressure and G is the generated pulse pressure.

Ontogenic change in normal fetuses

Altogether, 98 human fetuses were evaluated; the data from 18 fetuses were excluded because of poor recording due to fetal movements. The PWV and pulse pressure measurements from the remaining 80 fetuses are summarized in Figure 3. Among the normal fetuses, gestational age was significantly related to blood flow velocity ($0.032 \times GA + 0.097$; $r = 0.74$, $P < 0.01$), PWV ($0.115 \times GA\text{–}0.421$; $r = 0.7$, $P < 0.01$) and estimated pulse pressure ($0.814 \times GA\text{–}11.371$; $r = 0.74$, $P < 0.01$).

Effects of antenatal corticosteroids exposure

Twenty-one fetuses exposed to antenatal corticosteroids were available for analysis, and the fetal pulse pressures were evaluated on days 0, 2 and 8. One-

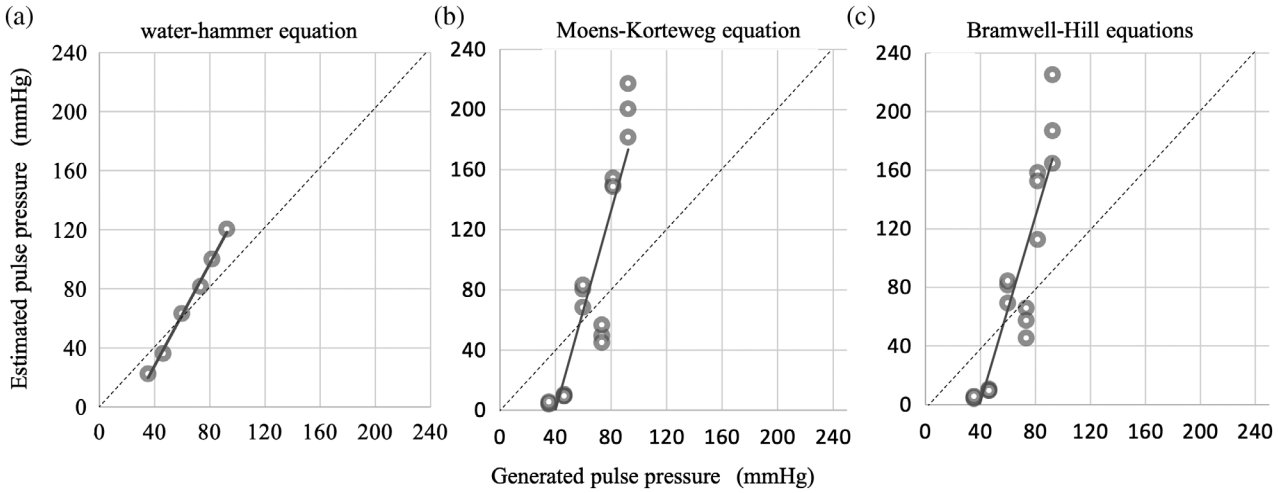

Figure 2 We compared the generated pulse pressure and estimated pulse pressures by each algorithm: (a) water hammer equation, (b) Moens-Korteweg equation, (c) Bramwell-Hill equation. The pulse generator changed the pulse pressure into six phases. The solid line is the regression line and the dashed diagonal line represents $y = x$. Regression line equations: water hammer equation: $y = 1.724 \times G\text{-}40.978$ ($r^2 = 0.99$, $P < 0.01$); Moens-Korteweg equation: $y = 3.315 \times G\text{-}134.07$ ($r^2 = 0.79$, $P = 0.054$); Bramwell-Hill equation: $y = 3.161 \times G\text{-}124.26$ ($r^2 = 0.80$, $P < 0.01$), where y is the estimated pulse pressure and G is the generated pulse pressure.

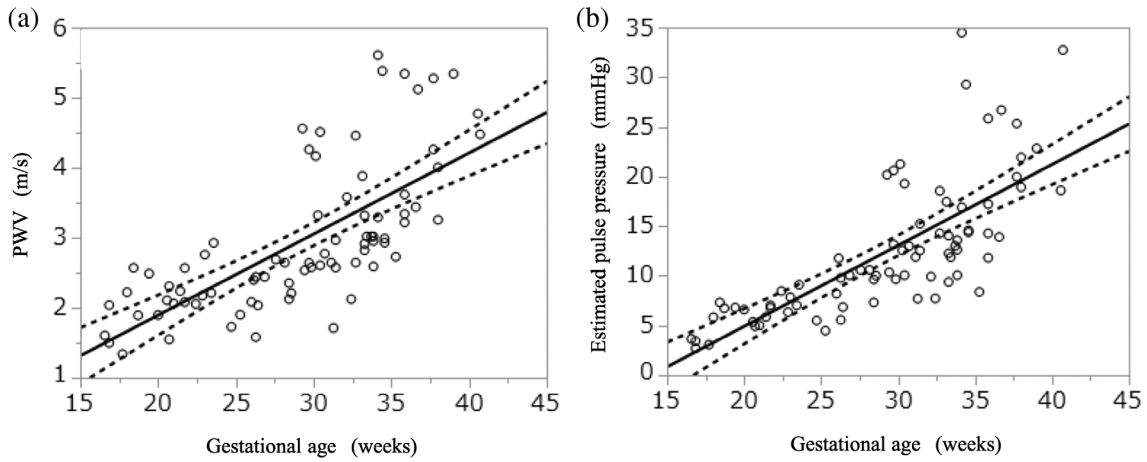

Figure 3 (a) Pulse wave velocity and (b) estimated pulse pressure in relation to gestational weeks in normal fetuses. The solid line represents the regression line, and the dotted lines indicate the 95% confidence interval. Regression line equations: pulse wave velocity = 0.115 × *GA*-0.421 (r = 0.70, $P < 0.01$); estimated pulse pressure = 0.814 × *GA*-11.371 (r = 0.74, $P < 0.01$), where *GA* is the gestational age (weeks).

way analysis of variance revealed a significant time effect on the estimated fetal pulse pressures in Figure 4 ($P< 0.01$). Although the fetal pulse pressures increased on day 2 (day 0, 15.02 ± 3.82 mmHg; day 2, 18.75 ± 5.15 mmHg; $P < 0.01$), they subsequently returned to baseline levels by day 8 (day 0, 15.02 ± 3.82 mmHg; day 8, 12.90 ± 4.71 mmHg; $P = 0.57$).

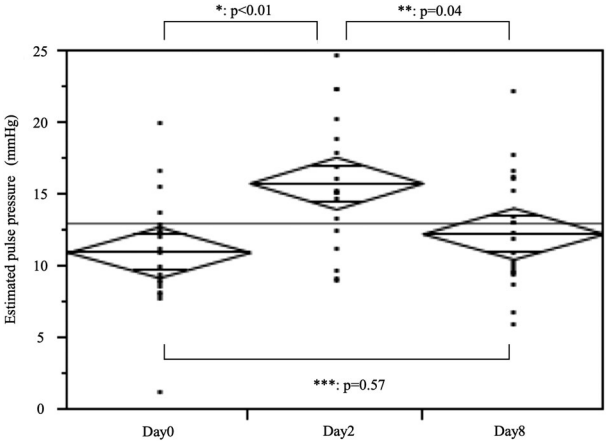

Figure 4 Pulse pressure evaluation in 21 fetuses who received antenatal corticosteroid. Measurement was performed before (day 0), 2 days after (day 2) and 8 days after (day 8) drug administration. *$P < 0.01$, **$P = 0.04$, ***$P = 0.57$. The kite diagrams show the mean (mid-lines) and 95% confidence interval for days 0, 2 and 8. The overall mean is the line across the middle of the figure.

Discussion

In this study, we evaluated the precision and feasibility of a method for estimating the fetal pulse pressure in the descending aorta using PWV and the ultrasonic phased-tracking method as well as blood flow velocity using the conventional pulse Doppler technique. The precision and accuracy of the method were verified using a circulation simulation model. An age-related increase in the pulse pressure in human fetuses was found, and exposure to exogenous corticosteroids was determined to have short-term effects on fetal pulse pressure. Our noninvasive approach is a feasible and clinically useful method for evaluating fetal hemodynamics.

Noninvasive assessment of fetal hemodynamic parameters, such as arterial pulse pressure from PWV at the descending aorta, have attracted attention; however, no studies have confirmed the accuracy of the estimated values.[5,6,10] Therefore, we designed a simulator of blood flow and estimated pulse pressure using each equation. The measured figures using the water hammer equation exhibited a strong correlation with the generated pulse pressures. Struijk *et al.*[5] have reported that fetal pulse pressure can be derived from measurements of PWV and vessel diameter changes in the fetal descending aorta using the Bramwell-Hill equation. They also estimated the distensibility and compliance of the fetal aortic wall, which became the basis of the first noninvasive estimation of arterial pulse pressure in human fetuses

using an echo-tracking system for detecting changes in vessel diameter.[11] However, their calculated fetal pulse pressures were widely distributed and poorly correlated with gestational age, which might be related to the limited accuracy of conventional ultrasonography systems and algorithm. In contrast, we employed ultrasonic phased-tracking method, which allowed us to assess the arterial wall's motion at the micrometer level.[12,13] The phased-tracking method uses small differences in raw radiofrequency signals to monitor these changes and provides greater precision (than that of conventional ultrasonography systems) by simultaneously recording radiofrequency signals from different beam directions, which provides a more precise evaluation of fetal PWV.

We used the water hammer equation for the present study and created a basic simulation, which revealed that our estimated pulse pressures were tightly correlated with the generated pressures in the phantom. The water hammer equation, which was derived from Newton's law of motion (as were the Moens-Korteweg and Bramwell-Hill equations), relates the time increment in blood flow velocity to the time increment in pulse pressure.[14] However, the water hammer equation requires the blood flow velocity (including PWV) measurement, while the Moens-Korteweg and Bramwell-Hill equations rely on diameter measurements. Basic experimental studies have revealed that the elastic behavior of the arterial wall exhibits nonlinear pressure dependency, which might introduce error in the diameter-dependent estimates from the Moens-Korteweg and Bramwell-Hill equa.[15,16] We previously reported on fetal pulse pressure estimations based on the Moens-Korteweg equation using ultrasonic phased-tracking method, but the measured fetal pulse pressure (51.0 ± 6.8 mmHg) was much higher than that expected in growth-restricted fetuses and the calculated fetal pulse pressures poorly correlated with gestational age.[6] In addition, there was a discrepancy between each non-invasive fetal pulse pressure assessment and invasive study for human fetuses.[5–7,10] Only the results of this study correlated with gestational age and were consistent with the expected values from invasive study.[7]

Blood pressure and related factors were well studied in human adults.[17] Arterial pressure is determined by the volume ejected by the heart into the arteries, arterial wall elasticity and systemic vascular resistance. If the arterial wall's elastic properties remain unchanged, pulse pressure would exhibit a good correlation with systolic and mean blood pressures and stroke volume.[18] In this regard, fetal pulse pressure is a function of the systolic and mean blood pressure and is dependent on stroke volume and placental vascular resistance. Although fetal blood pressure could not be directly measured, pulse pressure could be a very important clinical indicator of systolic and mean blood pressure, stroke volume and placental vascular resistance during fetal development.

Fetal pulse pressure measurement has the potential to contribute to fetal care, such as decreasing the incidence of neurological damage among infants. The brain has a high metabolic demand, and therefore, high cerebral blood flow is required. Experimental and clinical data suggest that hypoxemia alone does not induce brain damage and that corresponding cerebral ischemia is necessary for brain tissue injury.[1] The cerebral vasculature responds to ischemia through a hemodynamic protective process known as cerebral autoregulation, which involves adaptation of vascular resistance. The fetal cerebro-placental Doppler ratio and the middle cerebral artery Doppler, which reflect cerebral autoregulation, could predict adverse outcome.[19] However, routinely evaluating cerebro-placental Doppler ratio and/or middle cerebral artery Doppler in low-risk population would lead to substantial number of false negatives; furthermore, cerebral autoregulation may be impaired in patients with intracranial hemorrhage and ischemic stroke, especially those with very low birthweights.[19,20] Studies on premature neonates that focused on blood pressure suggested that systemic hypotension is an independent risk factor for intraventricular hemorrhage, developmental delay and mortality.[21-23] Therefore, not only cerebro-placental Doppler ratio and middle cerebral artery Doppler assessment but also fetal pulse pressure monitoring would potentially enable the detection of pathological hemodynamics leading to harmful events.

A study on isolated animal myocardium has revealed that fetal myocardium has less active tension than adult myocardium, resulting in lower maximal contractile force.[24] A recent study on human myocytes suggests that myofibril force production increases significantly as gestation progresses because of the maturation of the sarcomeres and the changes in contractile filament protein isoforms.[25] An invasive study determined that left and right ventricular pressures increase markedly as gestational progresses,[7] and a noninvasive echocardiographic study used the stroke volume of both ventricles, and the combined cardiac output, expressed as the sum of the left and

right ventricular cardiac outputs, increases in a linear fashion with advancing gestation in human fetuses.[7,26] These structural and functional development in the fetal myocardium may explain the increases in blood pressure and stroke volume as relating to the positive correlation of PWV and fetal pulse pressure with gestational age in this study.

To our acknowledge, this study is the first report that demonstrates a change in human fetal pulse pressure with antenatal steroid exposure. Antenatal steroid exposure increased the pulse pressure in animal fetuses and human adults. The vasopressor effects of corticosteroids have been observed in a pregnant sheep model, and several studies have identified similar vasopressor effects after short- and long-term corticosteroid use in adult humans.[27-30] Those studies found that corticosteroids increased cardiac output, renal vascular resistance, glomerular filtration rate, plasma volume, atrial natriuretic peptide concentrations and urinary kallikrein excretion as the cause of elevated blood pressure. Therefore, human fetal pulse pressure would be raised with antenatal steroid exposure just as in animal fetuses and human adults. The present study showed that fetal pulse pressure increased significantly on day 2 in response to maternal corticosteroid administration and that it returned to near control levels on day 8. We might think that our method is feasible for clinical practice and could potentially be used to obtain pulse pressure change in human fetuses.

This study had several limitations. First, measurement of blood density is quite difficult in fetuses. To date, no study has reported the gestational age-specific reference range for blood density. Second, the measurement of blood flow velocity was based on the Hagen-Poiseuille law. Theoretically, pulse pressure measurement requires accurate stroke volume and/or mean blood velocity in addition to PWV. The Hagen-Poiseuille law proves that the mean blood velocity is half of the maximum laminar flow velocity in steady state. However, it can be affected by blood viscosity and friction between the blood and the vessel walls. Third, the phased-tracking method cannot measure fetal PWV with any fetal or maternal movement. The phased-tracking method assesses the motion at the micrometer level, with even small movements leading to measurement error or misinterpretation. Hence, in the future, more accurate blood density and velocity measurement will improve blood pressure assessment in fetus.

In conclusion, we created an estimation model of pulse pressure using the water hammer formula, which consists of PWV and blood flow velocity that could precisely calculate the fetal pulse pressure. It could be used to monitor the normal development of fetal pulse pressure and determine the fluctuations in response to maternal corticosteroid administration. This noninvasive assessment of fetal pulse pressure would be a surrogate marker for fetal blood pressure and could be useful for the hemodynamic evaluation of compromised fetuses.

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Disclosure

None declared.

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