Doppler Audio Signal Analysis as an Additional Tool in Evaluation of Umbilical Artery Circulation

Doppler-Tonsignal-Analyse als zusätzliche Methode für Analyse der Durchblutung der Nabelarterie

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Abstract

Purpose: To investigate the predictive capacity of a new method for sound spectrum analysis of Doppler signals recorded from the umbilical artery in high-risk pregnancies.
Material and Methods: The retrospective study comprised 127 pregnant women with various pregnancy complications between 23 and 39 gestational weeks. Umbilical artery blood flow velocity waveforms were recorded with Doppler ultrasound and characterized by pulsatility index (PI) and blood flow class (BFC). Doppler audio signals were stored on a digital video recorder and the sound frequency at the energy level 15 dB below its peak (MAXpeak-15 dB) was estimated off-line. The prediction of probability for composite adverse pregnancy outcome (operative delivery for fetal distress, admission to neonatal intensive care unit, perinatal death) was evaluated using the area under the curve (AUC) of the receiver operating characteristics (ROC) curve.
Results: With increasing umbilical artery BFC, the MAXpeak-15 dB frequencies decreased ($p < 0.0001$) and the PI increased ($p < 0.0001$). The ROC AUCs for adverse outcome for MAXpeak-15 dB and for PI were 0.842 and 0.836 ($p = 0.88$), respectively. For the combination of MAXpeak-15 dB and PI, the corresponding AUC was 0.894, significantly higher than that of PI ($p < 0.03$) and of MAXpeak-15 dB ($p < 0.05$).
Conclusion: Umbilical artery Doppler sound spectrum analysis might be a useful supplement to PI in the clinical evaluation of fetoplacental circulation.

Zusammenfassung

Ziel: Die Untersuchung des prädiktiven Werts einer neuen Methode der Tonspektrum-Analyse von Dopplersignalen der Nabelschnurarterie in Hochrisikoschwangerschaften.
Material und Methoden: Die retrospektive Analyse beinhaltete 127 Schwangere mit unterschiedlichen Komplikationen zwischen der 23. und 39. Schwangerschaftswoche. Die Wellenformen der Blutflussgeschwindigkeit wurden mittels Dopplersonografie aufgenommen und durch den Pulsatilitätsindex (PI) und die Blutflussklasse (BFC) charakterisiert. Die Doppler-Tonsignale wurden auf einem digitalen Videorekorder gespeichert und als Off-Line wurde die Tonfrequenz mit einem Energieniveau von 15 dB unterhalb dessen Gipfel (MAXpeak–15 dB) veranschlagt. Die Vorhersage für einen kombinierten schlechten Ausgang der Schwangerschaft (operative Entbindung aufgrund fetaler Notlagen, Einweisung in eine neonatologische Intensivstation, perinatale Sterblichkeit) wurde mittels der „area under the curve“ (AUC) der ROC-Kurve (ROC) bewertet.
Ergebnisse: Mit steigender Nabelarterien-BFC sanken die MAXpeak–15dB-Frequenzen ($p = 0{,}0001$) und der PI stieg an ($p = 0{,}0001$). Bei schlechtem Ausgang betrugen die AUCs der ROC für den MAXpeak–15 dB 0,842 und für den PI 0,836 ($p = 0{,}88$). Bei der Kombination von MAXpeak–15 dB und PI war die entsprechende AUC mit 0,894 signifikant höher, als bei PI ($p < 0{,}03$) und MAXpeak–15 dB ($p < 0{,}05$) alleine.
Schlussfolgerung: Die Doppler-Tonsignal-Analyse der Nabelschnurarterie stellt neben dem PI eine nützliche Ergänzung für die klinische Bewertung der fetoplazentalen Durchblutung dar.

Introduction

The Doppler ultrasound technique has become an accepted method for antenatal surveillance of high-risk pregnancies. Doppler velocimetry provides important information on fetoplacental hemodynamics and makes it possible to follow the changes in fetoplacental circulation. The umbilical artery was the first fetal vessel to be examined by Doppler ultrasound [1] and is still one of the most important sources of information for the clinician in cases of placental insufficiency [2]. The umbilical artery blood velocity waveforms reflect placental resistance and are most often characterized by the pulsatility index (PI) [3].

Listening to the fetal heart tones with a stethoscope has always been a common procedure in the surveillance of the fetus and an important part of midwifery. Greenhill's textbook in obstetrics from the 1960 s describes that, while auscultating the heart sounds, a soft, blowing murmur might be heard. It emanates from the blood flow in umbilical arteries and is called fetal souffle [4]. In another textbook for midwives, the "funic souffle" is presented as a high-pitched sound synchronous with the fetal heart beats [5]. The author commented that hearing the funic souffle during labor may be a sign of fetal distress caused by nipping or tightening of knots in the cord.

In the late 1970 s and early 1980 s, the Doppler examinations of umbilical and uteroplacental circulation were performed blindly without support of two-dimensional (2 D) ultrasound images, using a stand-alone either continuous or pulsed Doppler velocimeter with a pen probe [1, 6 – 8]. The umbilical artery velocity signals were captured by listening to the Doppler signal, while adjustments of the insonation angle were performed. According to our experience, a skilled sonographer can perceive various timbres in the Doppler audio signals and distinguish different types of umbilical artery blood flow in fetuses with similar PI. Recently, we have developed and validated in an animal experimental model a method for objective analysis of the Doppler sound spectrum [9]. Subsequently, in a human pilot study, we compared the audio analysis and the traditional waveform analysis of umbilical artery Doppler signals before and after maternal steroid treatment [10]. The auditory parameter reflected the changes in the umbilical artery circulation more sensitively than the PI did.

Our hypothesis is that the auditory analysis of umbilical artery Doppler sound spectrum might be an additional tool in the evaluation of fetal circulation in high-risk pregnancies. The aim of the present study was to retrospectively apply the new auditory parameter on a group of high-risk pregnancies with various degrees of placental insufficiency in order to investigate its possible usefulness.

Materials and Methods

The study group comprised 127 singleton high-risk pregnancies with gestational age ranging from 23 to 39 weeks. They were referred for Doppler ultrasound examination according to the clinical fetal surveillance program. 101 (80 %) pregnancies were suspected of intrauterine growth restriction (IUGR) with fetal weight more than 2SD below the mean of expected weight according to the national standard intrauterine growth curve [11] and in 30 of them, there was concomitant preeclampsia (blood pressure ≥ 140/90 mm Hg and proteinuria ≥ 0.3 g/ in a 24-hour urine specimen with debut after 20 gestational weeks). 9 women had preeclampsia without IUGR, 6 women had insulin-dependent diabetes and 4 had essential hypertension. The remaining women were referred for ultrasound examination because of bad obstetric history (n = 8), decreased fetal movements (n = 2), pregnancy after in vitro fertilization (n = 2), sub-amniotic cysts of placenta and umbilical cord (n = 2), preterm prelabor rupture of membranes (n = 1) and hemorrhage in late pregnancy (n = 1).

Doppler ultrasound examinations of umbilical artery blood flow were performed using either a Philips HDI 5000 system with a 5 – 2 MHz probe (n = 45) or a Philips IU22 system with a 5 – 1 MHz probe (n = 82) (Philips Medical Systems, Bothell, WA). The two systems used Doppler ultrasound frequencies of 2.5 MHz and 2.3 MHz, respectively.

All Doppler examinations were done by an experienced sonographer (AT) following a strict protocol using a combination of real-time grayscale, color flow imaging and pulsed-wave Doppler together with auditory control of Doppler sounds for the optimization of the signals. Doppler signals were recorded from the free floating mid-portion of the umbilical cord. Color Doppler ultrasound was used to properly place the sample volume. The sample volume size was adapted to the vessel diameter in order to cover the vessel lumen. The high-pass filter was set to be as low as possible and the angle of insonation was kept close to 0°, never exceeding 20°. Final adjustment was done by listening to the audio signals in earphones (Sennheiser HD 480, Sennheiser Electronic GmbH, Wedemark, Germany) before accepting and storing the signals. All measurements were performed during periods of fetal inactivity, i. e. without fetal movements and fetal breathing movements, and during maternal voluntary apnea. There were no discernible uterine contractions.

Umbilical artery PI was calculated automatically on-line by the ultrasound equipment on 10 heart cycles of the Doppler sonogram with steady and uniform appearance. Doppler spectra together with umbilical artery Doppler audio signals were stored on a digital video recorder. In addition, the umbilical artery flow velocity waveforms were described semiquantitatively using the clinically established blood flow classes (BFC) [12]. Waveforms of BFC normal have positive diastolic flow and PI ≤ mean + 2SD of the reference curve [13]; BFC I, positive diastolic flow and PI > mean + 2SD and ≤ mean + 3SD; BFC II, positive diastolic flow, PI > mean + 3SD; BFC III, absent end-diastolic flow velocity. Umbilical artery waveforms with reverse end-diastolic flow were not included in the study.

The criteria for inclusion in the retrospective analysis were sufficient length (about 10 heart cycles) of the recording and storage both on the hard-drive of the ultrasound machine and on a digital video recorder. The recorded video clips were converted to avi-format and the audio information was exported as wav-files for off-line processing. Analysis of the wav-files was done blindly and in random order by an expert in audiology (KJB) using the software Adobe Audition (version 3.0; Adobe Systems Inc., San Jose, CA). A Fast Fourier Transform (FFT) was performed using a Hanning window with 2048 step size on the selected waveform sequence of Doppler sound spectrum. Analyses of the FFTs were done in the frequency range from 150 Hz, corresponding to the limit of earphones used by the sonographer, to 10,007 Hz, representing the frequency of the band stop of recording. An auditory feature, the high frequency cut-off band was identified within the frequency range [14]. Based on the results of our previous experimental study [9], this high-frequency cut-off ($MAX_{peak\text{-}15\,dB}$) was defined as the frequency band where the energy level had decreased by 15 dB from its maximum level, i. e. from the MAX_{peak} value (**Fig. 1**).

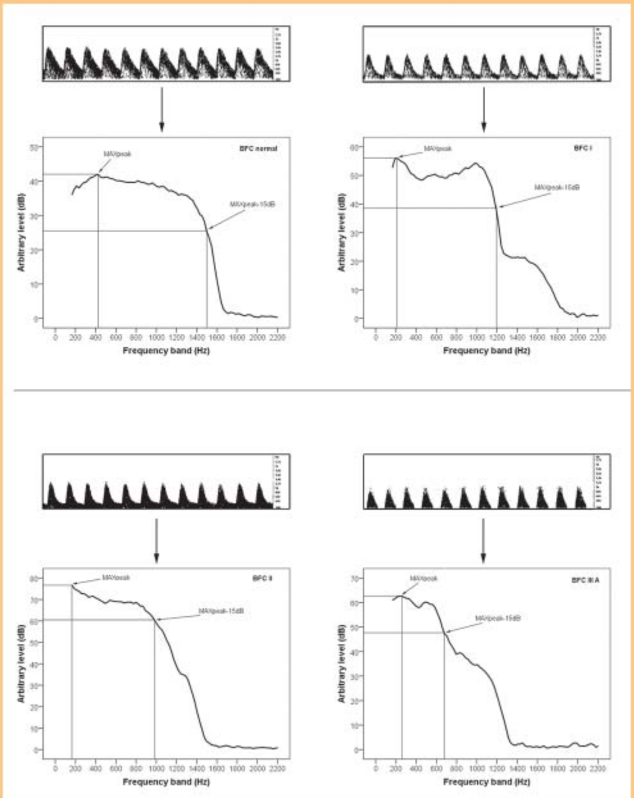

Fig. 1 Doppler audio analysis of umbilical artery Doppler signals recorded from four fetuses with various degrees of placental resistance described by blood flow classes (BFC). The Doppler ultrasound spectra are presented in the upper part of each panel, and the diagrams in the lower parts show the results of audio analysis. The arrows indicate the frequency bands with the highest energy (MAX_{peak}) and frequency bands where the energy has dropped by 15 dB from the maximum peak ($MAX_{peak\text{-}15\,dB}$).

Abb. 1 Doppler-Tonanalyse der Dopplersignale der A. umbilicales aufgezeichnet bei vier Feten mit unterschiedlichen Graden des Plazentawiderstands, der durch die Blutflussklassen (BFC) beschrieben wird. Die Doppler-Spektren sind im oberen Teil jeder Tafel dargestellt, die unteren Abschnitte zeigen die Ergebnisse der Tonanalyse. Die Pfeile bezeichnen die Frequenzbänder mit der höchsten Energie (MAX_{peak}) und die Frequenzbänder, bei denen die Energie um 15 dB unter den maximalen Gipfel ($MAX_{peak-15\,dB}$) gefallen ist.

The primary outcome variable was the composite adverse pregnancy outcome including perinatal death, operative delivery for fetal distress and admission for treatment in the neonatal intensive care unit. The risk for a negative outcome, given a certain value for artery PI, auditory parameter $MAX_{peak\text{-}15\,dB}$, or combination of PI and $MAX_{peak\text{-}15\,dB}$, was calculated using logistic regression analysis. The receiver operating characteristic (ROC) curves were constructed, and the areas under the curves (AUC) were used for characterization of the predictive performance of umbilical artery PI and of the auditory parameter $MAX_{peak\text{-}15\,dB}$. The method proposed by DeLong *et al.* [15] was used to compute the variance of each AUC and the variance of the difference between two dependent AUCs, respectively.

Kruskal-Wallis test, Chi-square test and Pearson's correlation analysis were used for statistical evaluations as appropriate, using MedCalc version 9.1.0.1. statistical package (MedCalc Software, Mariakerke, Belgium). The ROC curves were constructed and the AUC was calculated using Gauss (Gauss^{TM}; Aptec Systems Inc., Maple Valley, WA, USA; http://www.aptech.com).

The study has been approved by the Regional Research Ethics Committee at Lund University and the patients were given oral information about the Doppler examination.

Results

40 of the 127 fetuses had normal umbilical artery BFC, 24 had BFC I, 38 had BFC II, and 25 fetuses had BFC III (absent end-diastolic flow). The perinatal outcome of pregnancies is presented in **Table 1**. The composite adverse pregnancy outcome was found in 70 cases. There were 3 stillbirths and one very preterm infant died within one week after birth. 3 additional extremely preterm infants died at 22 days, 33 days and 6 months after birth, respectively. The causes of their death were necrotizing enterocolitis in the first two infants and chronic lung disease in the third infant.

With increasing BFC, we found a significant decrease of umbilical artery $MAX_{peak\text{-}15\,dB}$ frequencies ($p < 0.0001$) and a significant increase of PI ($p < 0.0001$) (**Table 2**). The individual values of umbilical artery $MAX_{peak\text{-}15\,dB}$ frequencies according to BFC are presented in **Fig. 2**. The correlation coefficient r between $MAX_{peak\text{-}15\,dB}$ and PI was –0.46 (95 % confidence interval -0.31 to -0.58).

The AUCs are presented in **Fig. 3**. The AUCs of the ROC curves for composite adverse outcome for the PI and for $MAX_{peak\text{-}15\,dB}$ were 0.836 and 0.842, respectively, and did not differ significantly ($p = 0.88$). The combined ROC, including both the umbilical artery $MAX_{peak\text{-}15\,dB}$ and PI, had an AUC of 0.894 that was significantly higher than the AUC of PI ($p < 0.03$) and that of $MAX_{peak\text{-}15\,dB}$ ($p < 0.05$).

Discussion

The new method for auditory analysis of umbilical artery Doppler signals has been applied on a clinical material of high-risk pregnancies. The auditory parameter $MAX_{peak\text{-}15\,dB}$ frequency was found to perform similarly to the traditional PI in predicting the probability of composite adverse pregnancy outcome. The predictive performance, characterized by the AUC of ROC curve, was improved when the two parameters were combined, suggesting that the $MAX_{peak\text{-}15\,dB}$ frequency might provide additional clinically useful information on the hemodynamics of fetoplacental circulation.

The new analysis method has been developed based on the observation that the timbre and pitch of umbilical artery Doppler sound signals might differ between fetuses, even if the waveforms of the maximum velocity curve are similar with the same PI, and that the different sounds are related to different pregnancy outcomes. In the early days of obstetric Doppler velocimetry, it was hoped that the estimation of volume blood flow in the umbilical vein [16] and/or fetal aorta [17, 18] would be the clinically useful tool for evaluation of fetoplacental circulation. Unfortunately, due to the relative inaccuracy of vessel diameter measurements and difficulty in estimating the time-average mean velocity (TAM), volume flow estimation was never adopted in clinical practice [19] and was replaced by a much easier waveform analysis of arterial maximum velocity. The velocity waveform reflects mainly the resistance to flow distal to the site of measurement and is only weakly related to the volume flow [20]. In our ani-

Table 1 Perinatal outcome in relation to umbilical artery blood flow classes (BFC), median (range) or n [%].

	umbilical artery blood flow classes				
	BFC normal n = 40	**BFC I n = 24**	**BFC II n = 38**	**BFC III n = 25**	**significance of difference (p-value)**
gestational age at delivery (weeks)	37 (25 – 42)	36 (23 – 38)	33 (24 – 40)	26 (23 – 35)	< 0.0001
birth weight (g)	2597 (625 – 4310)	1953 (494 – 3370)	1567 (425 – 2655)	690 (340 – 1598)	< 0.0001
birth weight deviation[1] (%)	−18 (−43 – + 21)	−26 (−38 – + 13)	−31 (−55 – −11)	−31 (−60 – −16)	< 0.0001
SGA	15 [38]	15 [63]	33 [87]	23 [92]	< 0.0001
female gender	16 [40]	12 [50]	21 [55]	10 [40]	0.49
preterm < 37weeks	18 [45]	11 [46]	23 [61]	25 [100]	0.0001
cesarean section	21 [53]	17 [71]	30 [79]	24 [96]	0.001
– emergency	14 [35]	14 [58]	27 [71]	24 [96]	< 0.0001
– elective	7 [18]	3 [13]	3 [8]	0	0.14
apgar score < 7 at 5 min	3 [8]	1 [4]	5 [13]	7 [28]	0.05
NICU admission	15 [38]	14 [58]	25 [66]	24 [96]	< 0.0001
perinatal mortality	1 [3]	0	2 [5]	1 [4]	0.69
composite adverse pregnancy outcome[2]	13 [32]	9 [38]	25 [66]	23 [92]	< 0.0001

SGA: small-for-gestational age (birth weight <mean-2SD of the standard curve [11]); NICU: neonatal intensive care unit. BFC normal, positive diastolic flow and PI ≤mean+ 2SD of the reference curve [12]; BFC I, positive diastolic flow and PI >mean+ 2SD and ≤mean+ 3SD; BFC II, positive diastolic flow, PI >mean+ 3SD; BFC III, absent end-diastolic flow velocity.
[1] Deviation from the expected mean for the gestational age according to the standard [11]);
[2] Operative delivery for fetal distress and/or admission to NICU for treatment and/or perinatal death.

Table 2 Results of Doppler spectrum and sound spectrum analysis of umbilical artery flow velocity signals according to umbilical artery blood flow classes (BFC).

	BFC normal n = 40	**BFC I n = 24**	**BFC II n = 38**	**BFC III n = 25**
pulsatility index				
mean ± SD	1.06 ± 0.22	1.40 ± 0.14	1.75 ± 0.24	2.72 ± 0.39
median (range)	1.04 (0.67 – 1.53)	1.40 (1.17 – 1.71)	1.75 (1.4 – 2.13)	2.67 (2.1 – 3.44)
auditory parameter $_{MAXpeak-15\,dB}$ (Hz)				
mean ± SD	1221 ± 355	1056 ± 270	1060 ± 277	849 ± 175
median (range)	1207 (539 – 2367)	1055 (352 – 1594)	1031 (445 – 1664)	867 (323 – 1148)

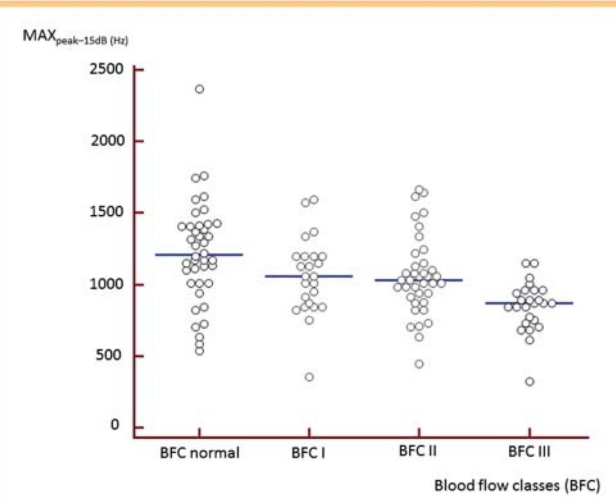

Fig. 2 Plot diagram of umbilical artery $MAX_{peak\text{-}15\,dB}$ frequencies according to blood flow classes (BFC). For definition of BFC, see the text.

Abb. 2 Punkte-Diagramm der $MAX_{peak-15dB}$-Frequenzen der Nabelarterie nach Blutflussklassen (BFC). Siehe Text für Definition der BFC.

mal experiments, the correlation coefficient between the $MAX_{peak\text{-}15\,dB}$ and TAM (r = 0.96) was higher than that for correlation between the TAM and PI (r = -0.79) [9]. This, in combination with the present finding of a weak correlation between the $MAX_{peak\text{-}15\,dB}$ and PI (r = -0.46), indicates that the new acoustic variable and PI do not measure the same feature of the Doppler signal and that the $MAX_{peak\text{-}15\,dB}$ is closer to the original goal of obstetric Doppler velocimetry, i. e. to the volume blood flow, than waveform analysis is.

Interestingly, already in one of the very first publications on the clinical use of Doppler ultrasound, Strandness and colleagues stated that "an observer, by listening to the amplified shifted frequencies with headphones or a loudspeaker, can learn to distinguish characteristics of various flow velocity signals" [21]. In the two very first reports on the application of Doppler ultrasound to examinations of blood flow in the umbilical artery, the authors described their use of earphones for adjusting and optimizing the recording [1, 6]. Use of stereo earphones also allows differentiation between positive and negative (reverse) signals by ear. After the advent of modern ultrasound techniques combining high-resolution imaging, color Doppler imaging and pulsed Doppler, listening to the signals has been generally abandoned in favor of adjusting the recording situation and optimizing signals by visual control of the Doppler spectrum. Indeed, modern ultrasound systems do not provide an output for audible signals anymore and the quality of built-in loudspeakers is usually very poor.

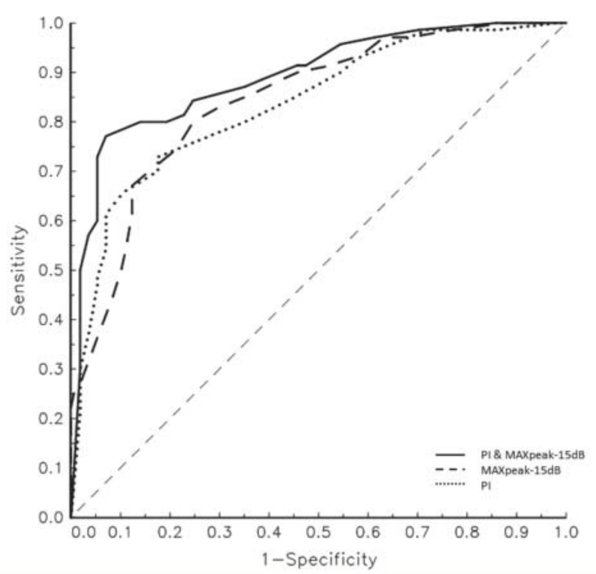

Fig. 3 Receiver-operating characteristic (ROC) curves for the prediction of composite adverse pregnancy outcome. Areas under the curve (AUC) were 0.836, 0.842, and 0.894 for the pulsatility index (PI), MAXpeak-15 dB and for the combined parameter (PI & MAXpeak-15 dB), respectively.

Abb. 3 „Receiver-operating characteristic"- Kurven (ROC) für die Vorhersage eines kombinierten schlechten Schwangerschaftsausgangs. Die "areas under the curve" (AUC) betrugen für die Parameter Pulsatilitätsindex (PI) 0,836 und für MAXpeak–15 dB 0,842 sowie für deren Kombination (PI & MAXpeak–15 dB) 0,894.

The evaluation of Doppler sound signals by ear is very subjective, highly dependent on the skills and experience of the operator. Consequently, the subjective method is not suitable for more general application. Therefore, we have developed an objective method of analyzing Doppler audio signals and we have identified a new parameter characterizing the sound signal – the maximum frequency at the energy level that is 15 dB below the peak ($MAX_{peak\text{-}15\,dB}$). This new characteristic of the sound signal proved to correlate very well with the subjective classification by operator, both for computer-simulated sound frequencies [22] and for umbilical artery signals recorded from sheep fetuses under various degrees of experimental asphyxia [9].
Obstetric Doppler velocimetry has improved the clinical surveillance of fetuses in high-risk pregnancies, especially in pregnancy complications due to placenta dysfunction [2]. The clinical use of Doppler umbilical artery recordings leads to a decrease in perinatal mortality and to a more rational obstetric management [23]. However, in many situations, like in very preterm cases of IUGR [24, 25] or in term and post-term pregnancies [26], definitive management protocols have not yet been established. Analysis of audio signals from the umbilical artery is not intended to replace the rather robust indices like PI. However, it can have additional supporting value in such situations. Software calculating the probability of adverse outcome based on the combined evaluation of PI and $MAX_{peak\text{-}15\,dB}$ should easily be made available.
The present study has some limitations. It is retrospective and the small number of pregnancies does not allow definite conclusions about the possible clinical value of the new method. The analysis of audio signals is automatic. However, the reproducibility of the whole procedure, including the recording of Doppler signals and selection of the representative recording segments for analysis, has not been tested yet.
During the study, two ultrasound systems with different Doppler ultrasound frequencies were used for recording umbilical artery flow signals. As the Doppler shift frequencies are proportional to the transmitted frequency, we considered adjusting the resulting sound spectrum measures accordingly. However, when we tested the two systems side by side using a flow phantom, the recorded velocities did not reflect the difference in ultrasound frequencies (unpublished). We assumed that the technical features of modern ultrasound instruments, such as sensitivity, signal processing, and variations in sample volume, overshadowed the 9 % difference in transmitted Doppler frequency. Therefore, we abstained from any post hoc corrections.
Among the strengths of the study, probably the most important is the good quality of primary Doppler signals recorded by a single experienced operator according to a standard protocol. Furthermore, the material comprised a wide range of pregnancy complications and various types of umbilical artery blood flow such as all BFCs were represented. The cases with reverse end-diastolic flow were not included as they present a very typical "pounding" sound, profoundly different from the soft murmur of the pulsations with positive diastolic flow. It has been shown that the various degrees of reverse diastolic flow could be differentiated by a detailed and quantified analysis of the maximum velocity waveform and that there was an association with the outcome [27]. However, the clinical finding of reverse diastolic flow is considered indicative of severe fetal compromise and constitutes an indication for delivery, largely disregarding the gestational age [24]. Thus, performing a sophisticated analysis of the Doppler sound does not seem meaningful in such cases.
When evaluating the single outcome variables in the present study, e. g. low Apgar score, operative delivery for fetal distress or admission to NICU, we found that the predictive performance of PI and $MAX_{peak\text{-}15\,dB}$ was not significantly different (data not shown). However, in a sub-cohort of pregnancies with BFC normal ($n = 40$), for the prediction of SGA at birth, a surprisingly large AUC (0.80) was found for the auditory parameter. This potentially interesting application should be tested in a larger cohort.
In summary, the study showed that the new way of analyzing the umbilical artery Doppler sound signals might have clinical potential and that the auditory parameter, $MAX_{peak\text{-}15\,dB}$, seems to be promising as a supplement to the traditional waveform analysis in the assessment of fetal circulation. Before evaluating the possible clinical usefulness of the new method in larger prospective studies, it is important to further develop the techniques facilitating the transfer of sound signals and their auditory analysis. Moreover, gestational age-related standards for $MAX_{peak\text{-}15\,dB}$ and reproducibility of the measurements should also be established.
It might be of interest to note here that, in the future, three-dimensional ultrasound technology will an excellent application area have in Doppler examinations, i. e., angle correction, and precise sample volume location can be fully automated, thus making the sound signals easily accessible and much less dependent on operator skills.

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