Use of sound-elicited fetal heart rate accelerations to assess fetal hearing in the second and third trimester

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Abstract

Objectives: We previously reported that fetal heart rate (FHR) accelerations could be obtained after fetal sound stimulation. We examined FHR accelerations during 20 to 37 weeks gestational age (GA) in order to assess the optimal time for the test.

Methods: The fetus was stimulated from the maternal abdomen with pure tone 2000 Hz, 90 dB, 5 seconds. Changes in the FHR before and after the sound stimulation were measured by a cardiotocometer.

Results: Compared with the positive rate of FHR accelerations at 20 to 21 weeks GA, significant increases were recognized in 26 to 27, 28 to 29, 30 to 31, and 34 to 35 weeks GA. Comparing the positive rate of FHR accelerations between the minimal and moderate variability of FHR baseline, no significant differences were observed at 20 to 27 weeks GA. On the other hand, at 28 to 37 weeks GA, the positive rate to detect FHR accelerations due to sound stimulation was 100% in moderate FHR baseline variability.

Conclusion: Considering development of human fetal hearing, the method should be performed between 28 to 37 weeks GA and during moderate FHR variability corresponding to active sleep conditions. The method developed in the present study may provide a promising tool for evaluating the fetal hearing.

Keywords: fetus, fetal heart rate variability, hearing test, heart rate acceleration, sound stimulation
Introduction

A number of studies have revealed that the human fetus is able to hear and that acceleration of the fetal heart rate (FHR) occurs in response to sound stimulation [1-4]. However, there are few studies aimed at the practical application of a fetal hearing test.

We established technically advanced sound stimulation and delivery systems using energy harvesting devices. Cardiac responses induced by vibroacoustic stimulation may be mediated by the vestibular hair cell and cutaneous receptors in addition to the cochlear hair cells. However, the piezoelectric vibration system produces minimal vibration on the body surface, and exposes the mother to little sound noise. We found that tones of middle and high frequency of less than moderate intensity were likely to be more suitable for the fetal auditory examination and that the piezoelectric vibrator-stimulated potential responses accelerated the heart rate of the fetus with consistent and reproducible manners. Thus, we have reported that, when developing a stimulation system for a fetal hearing test, in fetuses between 32 to 37 weeks gestational age (GA), the FHR after 70 dB sound stimulation increased in all cases compared to before stimulation [5]. However, a critical GA to detect fetal hearing has not yet been obtained.

In the present study, we conducted research aimed at establishing a fetal hearing test using the fetal sound stimulus system. The optimal time for the test and factors affecting the test were investigated at 20 to 37 weeks GA. The goal was determine the optimal testing period and factors affecting the test were investigated for assessing normal hearing fetuses.

Materials and methods

To examine the FHR accelerations elicited by sound stimulation, a total of 39 fetuses of different GA from low-risk pregnant women participated, and multiple measurements were taken. Seven fetuses at 20 to 21 weeks GA, 6 at 22 to 23 weeks GA, 8 at 24 to 25 weeks GA, 11 at 26 to 27 weeks GA, 10 at 28 to 29 weeks GA, 17 at 30 to 31 weeks GA, 11 at 32 to 33 weeks GA, 12 at 34 to 35 weeks GA, 1 at 36 to 37 weeks GA were enrolled. All pregnancies were singletons. The normal hearing of all fetuses was confirmed at birth by neonatal hearing screening using automated auditory brainstem response. The study protocol was approved by the Juntendo Hospital. The pregnant women provided informed, written consent for themselves and their fetuses prior to participation.

Fig. 1 shows the measurement system for the FHR variance. The sound stimulus system consisted of a function generator (WF1944, NF Corporation, Kanagawa, Japan), a personal amplifier (AP15d, Fostex, Tokyo, Japan), and a giant magnetostrictive material (GMM) vibrator (custom-made, Shonan Metaltec, Kanagawa, Japan). Auditory signals generated by the function generator are amplified by the personal amplifier and are input into the GMM vibrator. The same procedure as in the previous study [5] was used to determine whether the pressure generated in the uterus was correct based on a model of the mother's abdomen. FHR variance was measured by a tocomonitor (Avalon FM20, ATOM Medical, Tokyo, Japan). The test signal 2000 Hz at a level of 90 dB with 5 sec duration was presented 3 times with an interval of 1 minute or more. Just before the sound stimulation, the obstetrician used ultrasound to check the health and position of the fetus and to mark the position of the head and heart of the fetus. Pregnant women who had eaten before the examination were excluded. The pregnant women lay on a bed in a soundproof room. In order to avoid any interference from the mother, she was
supplied with head-phones presenting relaxing music that masked the sound. The head position of the fetus was determined by ultrasound and the stimulator was placed on the maternal abdomen just above the fetus head. The probe of a tocomonitor was placed in a position where the fetal heart beats were best detected. The subjects had rested 3 minutes before starting the experiment, during which time the heart rate of the fetus was recorded. A typical FHR acceleration recording is shown in Fig. 2. FHR accelerations often occurred with fetal movement or contraction of the uterus. Thus, the following criteria for the judgement of positive FHR changes were decided upon. We defined FHR acceleration elicited by sound stimulus as one that occurred within 60 seconds and continue 10 to 120 seconds after the stimulus [5]. Moreover, the amplitude of the FHR acceleration was defined as 10 bpm or more at 20 to 31 weeks GA, and 15 bpm or more at 32 to 37 weeks GA [6]. The sound stimulation was carried out three times. A positive response was defined as the presence of a FHR acceleration at least once. The FHR baseline before sound stimulation was volatile. Therefore, the FHR baseline condition for 3 minutes before the sound stimulation was divided into a minimal FHR variability: amplitude range \( \leq 5 \) bpm and a moderate FHR variability: amplitude range of 6 bpm to 25 bpm [6]. The minimal and moderate FHR variability is defined as quiet and active sleep, respectively [7-9].

SAS 9.4 software (SAS Institute, Cary, NC) was used for all statistical analyses. The relationship between GA and FHR acceleration was tested by the Cochran-Armitage trend test. The positive rate of the FHR acceleration was compared with weeks GA, FHR baseline condition, pre-pregnancy body mass index, alcohol consumption, maternal age, fetal gender, and gynecological history by Fisher’s exact test. Differences were considered to be significant if \( p < 0.05 \).

**Results**

The FHR accelerations due to the sound stimulation were recognized from 20 weeks GA. Three of 7 fetuses during 20 to 21 weeks GA, 3 of 6 during 22 to 23 weeks GA, 5 of 8 during 24 to 25 weeks GA, 10 of 11 fetuses during 26 to 27 weeks GA, 10 of 10 fetuses during 28 to 29 weeks GA, 15 of 17 fetuses during 30 to 31 weeks GA, 7 of 11 fetuses during 32 to 33 weeks GA, 12 of 12 fetuses during 34 to 35 weeks GA, 1 of 1 fetus during 36 to 37 weeks GA, showed FHR accelerations (Fig. 3). The positive rate of FHR accelerations, ranging around 50% in 20 to 25 weeks GA, abruptly increased from 26 weeks GA. There is a clear trend that more acceleration was detected in older fetuses \( (p=0.0037) \). Compared with the positive rate of FHR accelerations during 20 to 21 weeks GA, significant increases were recognized during 26 to 27, 28 to 29, 30 to 31, and 34 to 35 weeks GA.

The relationship between FHR accelerations and the FHR baseline variability is shown in Fig. 4. Irrespective of the sleep conditions, the positive rate of sound-elicited FHR accelerations was unstable during 20 to 27 weeks GA. Comparing the positive rate of FHR accelerations between the minimal and moderate variability in the FHR baseline, no significant differences were observed in 20 to 27 weeks GA. At 28 to 37 weeks GA, in all the subjects showing no FHR acceleration there was minimal variability in the FHR baselines, indicating quiet sleep.

The positive rate of the FHR acceleration was not correlated with pre-pregnancy body mass index, alcohol consumption, maternal age, fetal gender, or gynecological history (Table 1).
Discussion

In the present study, the fetuses after 28 weeks GA in active sleep conditions showed sound-elicited FHR accelerations, suggesting the capability of sound perception. Several subjects after 28 weeks GA without sound-elicited FHR accelerations could be explained by quiet sleep conditions corresponding to minimal FHR baseline variability. The extent of central nervous system arousal is quite different between quiet and active sleep [10]. Arousal is controlled by broad-based structures within the mesencephalic reticular formation. Sensory input such as auditory perception to the mesencephalic reticular formation activates the cortical system coincident with control of heart rate changes via the brainstem. Active sleep is characterized by widespread activation of brain structures. Therefore, it is possible that differences in the sound-elicited FHR accelerations between active and quiet sleep may be explained.

On the other hand, the presence and absence of FHR accelerations were independent of the FHR baseline variability, namely sleep conditions, during 20 to 27 weeks GA. Regarding the development of human fetal hearing, previous studies have reported that the auditory brainstem response occurs in premature infants at 25 to 28 weeks GA [11-13], and the appearance of otoacoustic emissions at 33 weeks GA [14]. Thus, the unstable appearance of sound-elicited FHR accelerations during 20 to 27 weeks GA may be brought about by individual differences in the development of auditory pathways.

Based on our series of animal experiments [15-18], Gjb2 mutant mice were characterized by profound deafness from birth, which corresponds to 26 to 28 weeks GA in humans. In order to discover hereditary deafness at an early stage, at least that related to the GJB2 mutation, prenatal diagnosis of deafness is required. Recently, genetic methods have been reported for the prenatal diagnosis of congenital hearing loss. Noninvasive prenatal testing (NIPT) for common aneuploidy (such as Down's syndrome) is clinically available as a screening test [19-21]. Chang et al. [22] reported NIPT for autosomal recessive congenital sensorineural hearing loss. Meng et al. [23] have reported a method of screening with high accuracy to determine whether a fetus has a homozygote of GJB2 with 235delC by haplotype analysis using maternal blood fetal DNA and familial DNA. The absence of sound-elicited FHR acceleration, suggesting evidence for deafness, may complement the diagnosis of hereditary deafness before birth by the NIPT technology. Further studies are required for practical applications.

This test can diagnose prenatal deafness before newborn hearing screening and timely management of prenatal deafness leading to better lives is feasible. This technology has clear standards and is easy to operate. It can be used by anyone, including otolaryngologists, obstetricians and gynecologists, pediatricians, midwives, and audiological technologists. Perform additional tests for hearing-impaired fetus and compare with normal hearing fetus further studies are required for practical applications.

Conclusion

Sound-elicited FHR accelerations, indicating the capability of sound perception, were obtained after 28 weeks GA in the presence of moderate FHR baseline variability.
The method developed in the present study may provide a promising tool to evaluate the fetal hearing.

**Disclosure statement**

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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**References**


Figure legends

Table 1. Effects of clinical profiles on the fetal heart rate acceleration

**Fig. 1.** Block diagram of the measurement system of sound-elicited fetal heart rate. Auditory signals generated by the function generator are amplified by the personal amplifier and are input into the giant magnetostrictive material (GMM) vibrator. The head position of the fetus was determined by ultrasound, and the stimulator was placed on the maternal abdomen just above the fetus head. The probe of a tocomonitor was placed in a position where the fetal heart beats were best detected.

**Fig. 2.** A representative trace of fetal heart beat waveform. The fetal heart rate (FHR) acceleration elicited by sound stimulus was defined as when it began within 60 s and continued 10 to 120 sec after the stimulus. Moreover, the amplitude of the FHR acceleration was defined as 10 bpm or more at 20 to 31 weeks gestational age and 15 bpm or more at 32 to 37 weeks gestational age.

**Fig. 3.** The positive rate of sound-elicited fetal heart rate acceleration in each gestational age. The positive rate was apparently increased after 26 weeks gestational age. Parentheses denote the number of subjects. n.s.: not significant; n.d.: not determined; *:p<0.05; **:p<0.01.

**Fig. 4.** The positive rate of sound-elicited fetal heart rate acceleration in 20 to 27 weeks gestational age in minimal (left columns) and moderate (right columns) fetal heart rate baseline variability. Black and open columns denote the presence and absence of the fetal heart rate acceleration, respectively. Parentheses denote the number of subjects. n.s.: not significant; n.d.: not determined; *:p<0.05; **:p<0.01.
Figure 1.
Figure 2.

Time (s) 0 40 80 120 150 200

Fetal heart rate (bpm)

FHR baseline

10 bpm or 15 bpm over

≤ 60 seconds

10 to 120 seconds

Stimulus

Start

Peak

End
Figure 3.
Figure 4.
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