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学位論文

Change in fetal behavior in response to vibroacoustic stimulation

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Abstract

Objective: To assess fetal behavioral changes in response to vibroacoustic stimulation (VAS) in normal singleton pregnancies using four-dimensional (4D) ultrasound.
Methods: Ten types of fetal movements and facial expressions in 68 healthy pregnant women between 24 and 40 weeks were studied using 4D ultrasound for 3 min before and after 3-s VAS. The frequencies of mouthing, yawning, tongue expulsion, back arch, jerky arm movement, startle movement, smiling, scowling, hand-to-face movement, and blinking were evaluated. The fetuses were subdivided into four gestational age groups (24–27, 28–31, 32–35, and ≥36 weeks). Comparison of the frequencies of the fetal behaviors before and after the stimulation in each gestational age group was conducted to detect the response to stimulation with advancing gestation.
Results: There were no significant differences in the frequency of each fetal behavior before and after VAS at 24–27, 28–31, and 32–35 weeks of gestation. However, the frequencies of blinking and startle movements were significantly higher after VAS in the 36–40 gestational age group ($P < 0.05$).
Conclusion: The age of 36 weeks of gestation might represent an advanced stage of brain and central nervous system development and maturation as the response to stimuli is prominent at this age compared with earlier gestation.

Keywords: 4D ultrasound; fetal behavior; fetal CNS development; fetal CNS maturation; fetal stress; vibroacoustic stimulation.

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Introduction

Vibroacoustic stimulation (VAS) is a simple non-invasive method to stimulate fetuses. Fetal heart rate acceleration following this stimulation was noted, and it has since been incorporated in fetal heart rate tracing for fetal well-being assessment *in utero* [1, 2], as well as intrapartum fetal surveillance [3, 4]. VAS has also been used to detect fetal response, and therefore to assess fetal hearing impairment [5, 6].

With advancements in ultrasound technologies, there have been numerous neurobehavioral studies to evaluate fetal movements and facial expressions as a direct method to determine the level of maturation and development of the fetal brain and central nervous system (CNS) [7–17]. There have been several studies on two-dimensional (2D) sonographic assessment of the fetal neurobehavioral response to VAS [18–26]. However, fetal behaviors outside the scanning plane cannot be displayed on the monitor when using 2D sonography [12]. To the best of our knowledge, no study has used four-dimensional (4D) ultrasound study to assess the fetal behavioral response to VAS. This study was conducted to evaluate the changes in the frequency of fetal movements and facial expressions after VAS using 4D ultrasound, to detect developmental changes in the fetal brain and CNS functions with advancing gestation.

Subjects and methods

The study was performed at Kagawa University Hospital during 2-year period from April 2016 to April 2018. Subjects of the study were recruited randomly from pregnant women matching the inclusion criteria among those who were receiving their ultrasound examination during routine antenatal care at the outpatient department during that time. Healthy pregnant non-smoker Japanese women between 24 and 40 weeks of gestation with singleton pregnancies were the targets of the study. Pregnancies associated with high maternal (gestational diabetes, hypertensive disorders of pregnancy, polyhydramnios, and thyroid disorders) or fetal risks (fetal growth restriction and chromosomal abnormalities) were excluded from the study. The present study received approval from the Kagawa University Graduate School of Medicine Ethics Committee. Participants were informed about the aim and methods of the study, and provided their informed consent.

Calculation of the gestational age was based on the last menstrual period confirmed by first-trimester sonographic examination. A total of 68 consecutive women matched our inclusion criteria and were enrolled in the study. Ten parameters including fetal facial expressions and behaviors were assessed using 4D ultrasound (Voluson E8, GE HealthCare Japan, Tokyo, Japan) and a curved array transabdominal transducer (4–8.5 MHz) with a maximum frame rate of 40 frames/s. These parameters included six facial expressions (mouthing, yawning, tongue expulsion, smiling, scowling, and blinking) in addition to four fetal body movements (back arch, jerky arm movement, hand-to-face movement, and startle movement). The components of these six facial expressions were described in detail in our previous study, which included the same facial expressions [17]. Initially a 3-min-recording was done followed by observation of these parameters for 3 min after vibroacoustic stimulator (TR-30, Toitsu, Yokohama, Japan) producing 30–80 Hz at 110 dB at 1 m in air, and acceleration up to 100 Gal, which was placed on the maternal abdomen for 3 s. The use of TR-30 is approved in Japan and it had been previously used in other studies concerned with fetal surveillance and behavior with no remarks upon its safety in these previous studies or our current study [27–30]. They were sub-classified into four gestational age groups to detect any change in fetal response to VAS with advancing gestation. During examination, sometimes applying VAS resulted in fetal startle and turning face away from the scanning plane; however, only cases with clear views allowing accurate analysis of the targeted fetal movements were included. Each case was examined only once. They were subdivided into four gestational age groups (13 fetuses at 24–27 weeks, 16 fetuses at 28–31, 15 fetuses at 32–35, and 24 fetuses ≥36 weeks). Table 1 shows the clinical characteristics of the study subjects in each group. One well-experienced operator (KO) performed all ultrasound examinations.

Comparisons of frequencies of fetal movements and expressions before and after VAS were evaluated using the Mann-Whitney U test. Differences in the gestational age at birth, birth weight, Apgar score (1 min, 5 min) and umbilical artery pH (UApH) were evaluated using the Kruskal-Wallis one-way analysis of variance. The chi-square test was conducted to assess differences in fetal sex and neonatal intensive care unit (NICU) admission among the four groups. IBM SPSS Statistics 22 (IBM SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A P-value < 0.05 was considered significant.

Results

There were no significant differences regarding the gestational age at birth, birth weight, fetal sex, Apgar score at 1 and 5 min, UApH, or NICU admission among the four groups of subjects (Table 1).

There was no statistically significant change in the frequencies of the ten fetal movements before and after VAS in the 24–27-week (Table 2), 28–31-week (Table 3), and 32–35-week groups (Table 4). However, in the 36–40-week group, blinking (median 1; range 0–7) and startle movement (median 1; range 0–4) showed significant increases in frequencies after VAS compared with before VAS [blinking: median 0; range 0–8 (Figure 1) and startle movement: median 0; range 0–4 (Figure 2) ($P < 0.05$)]. However, the remaining eight fetal movements showed no significant changes after VAS (Table 5).

Discussion

The fetus *in utero* is not in an isolated environment. Previous reports showed that fetuses exhibit facial expressions indicating pain or stress as a possible response to internal stimuli such as uterine synechia or physical contact with a twin [31, 32]. The fetal response to external stimuli

Table 1: Clinical characteristics of the subjects.

Gestational age group (weeks)	n	Gestational age at examination	Gestational age at birth	Birth weight	Sex	Apgar score		UApH	NICU admission, %
		weeks	weeks	g	male/female	1 min	5 min		
		Mean (SD)	Mean (SD)	Mean (SD)		Median (range)	Median (range)	Mean (SD)	
24–27	13	25.7 (1.0)	38.6 (2.7)	2802.5 (644.4)	9/4	8 (5–9)	9 (8–10)	7.29 (0.05)	8
28–31	16	29.6 (1.0)	39.6 (1.4)	3166.1 (435.4)	8/8	8 (7–9)	9 (8–10)	7.28 (0.07)	0
32–35	15	34.0 (1.0)	38.5 (1.4)	3208.9 (424.0)	6/9	8 (7–9)	9 (9–10)	7.26 (0.10)	7
36–40	24	37.5 (1.0)	40.0 (1.0)	3203.6 (342.9)	9/15	8 (2–9)	9 (8–10)	7.31 (0.06)	4
Significance			NS	NS	NS	NS	NS	NS	NS

SD, standard deviation; EFW, estimated fetal weight; UApH, umbilical artery blood pH; NS, not significant.

Table 2: Change in the frequency of each fetal movement after vibroacoustic stimulation at 24–27 weeks of gestation.

Fetal movement	Change in frequency Median (range)		Significance
	Before	After	
Mouthing	1 (0–5)	2 (0–11)	NS
Yawning	0 (0–3)	0 (0–1)	NS
Tongue expulsion	0 (0–0)	0 (0–1)	NS
Back arch	0 (0–1)	0 (0–1)	NS
Jerky arm movement	0 (0–0)	0 (0–0)	NS
Startle movement	0 (0–2)	1 (0–3)	NS
Smiling	0 (0–1)	0 (0–1)	NS
Scowling	0 (0–3)	0 (0–3)	NS
Hand-to-face movement	0 (0–4)	1 (0–4)	NS
Blinking	0 (0–3)	0 (0–7)	NS

NS, not significant.

Table 3: Change in the frequency of each fetal movement after vibroacoustic stimulation at 28–31 weeks of gestation.

Fetal movement	Change in frequency Median (range)		Significance
	Before	After	
Mouthing	2 (0–9)	3 (0–5)	NS
Yawning	0 (0–1)	0 (0–2)	NS
Tongue expulsion	0 (0–0)	0 (0–1)	NS
Back arch	0 (0–1)	0 (0–2)	NS
Jerky arm movement	0 (0–1)	0 (0–0)	NS
Startle movement	1 (0–2)	1 (0–3)	NS
Smiling	0 (0–1)	0 (0–3)	NS
Scowling	0 (0–3)	0 (0–1)	NS
Hand-to-face movement	0 (0–3)	1 (0–6)	NS
Blinking	0 (0–4)	0 (0–4)	NS

NS, not significant.

has been investigated as a method to evaluate neurobehavioral development through interaction and different responses to various external stimuli. The mother's voice and touching her abdomen elicited a fetal response [33]. The fetus reacts to lights and sounds applied to maternal abdomen [34]. Moreover, fetal facial expressions changed in response to intravaginal music [35]. The responses to these stimuli with advancement of gestation have been proposed as a method to assess functional development of the fetal brain and CNS. The current study investigated the changes in fetal behaviors and facial expressions following VAS with advancing gestation. Fetuses younger than 36 gestational weeks did not show any change in the frequency of these behaviors and facial expressions, whereas significant increases in the frequencies of blinking and startle movement were noted after 36 weeks of gestation. A possible explanation for this result involves the fetal behavioral state because the fetal response to a stimulus

Table 4: Change in the frequency of each fetal movement after vibroacoustic stimulation at 32–35 weeks of gestation.

Fetal movement	Change in frequency Median (range)		Significance
	Before	After	
Mouthing	1 (0–11)	2 (0–6)	NS
Yawning	0 (0–1)	0 (0–3)	NS
Tongue expulsion	0 (0–1)	0 (0–2)	NS
Back arch	0 (0–0)	0 (0–0)	NS
Jerky arm movement	0 (0–0)	0 (0–0)	NS
Startle movement	0 (0–1)	0 (0–2)	NS
Smiling	0 (0–2)	0 (0–2)	NS
Scowling	0 (0–3)	0 (0–2)	NS
Hand-to-face movement	0 (0–2)	0 (0–3)	NS
Blinking	0 (0–8)	0 (0–6)	NS

NS, not significant.

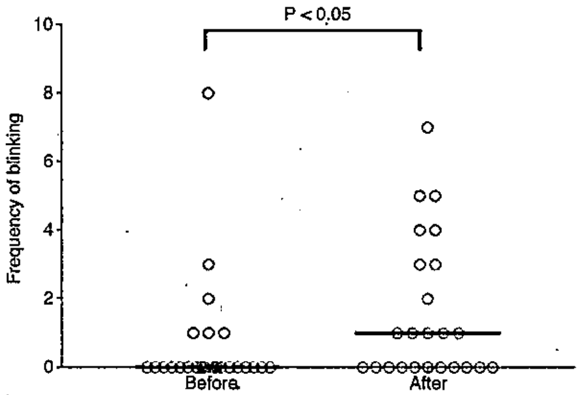

Figure 1: Comparison of the frequency of blinking before and after vibroacoustic stimulation at ≥36 weeks' gestation.

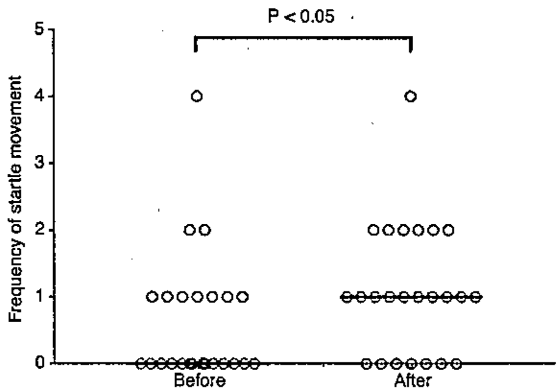

Figure 2: Comparison of the frequency of startle movement before and after vibroacoustic stimulation at ≥36 weeks' gestation.

Table 5: Change in the frequency of each fetal movement after vibroacoustic stimulation at 36–40 weeks of gestation.

Fetal movement	Change in frequency Median (range)		Significance
	Before	After	
Mouthing	1 (0–7)	1 (0–6)	NS
Yawning	0 (0–3)	0 (0–1)	NS
Tongue expulsion	0 (0–0)	0 (0–1)	NS
Back arch	0 (0–0)	0 (0–1)	NS
Jerky arm movement	0 (0–0)	0 (0–0)	NS
Startle movement	0 (0–4)	1 (0–4)	P<0.05
Smiling	0 (0–3)	0 (0–2)	NS
Scowling	0 (0–1)	0 (0–2)	NS
Hand-to-face movement	0 (0–2)	0 (0–2)	NS
Blinking	0 (0–8)	1 (0–7)	P<0.05

NS, not significant.

depends on the fetal behavioral state, which is known to be organized after 36 weeks of gestation [8]. Therefore, the difference in response to VAS is evident at 36 weeks representing a state of fetal neurodevelopmental maturation. Another explanation for the response in this age group is that the fetal response is dependent on development of the auditory system. Although it starts to function at around 26–28 weeks of gestation [36], a previous investigation documented a more marked response after 37 weeks probably due to functional maturation of the auditory system of the fetus [37]. This may explain the absence of a response in the youngest age group at 24–27 weeks whose auditory system has not yet developed, whereas the middle age groups (at 28–31 and 32–35 weeks) did not show responses to VAS due to incomplete functional maturation of the fetal auditory system. Other studies reported that the fetal motor response to VAS starts at 28 weeks and startle movement occurs at 30 weeks [38], while our study showed the response to occur after 36 weeks. In previous studies, startle reflex was found to be a response to VAS from 30 weeks of gestation [39]. The difference among previous and our studies might be due to variation in the intensity of the stimulus, as fetuses at an earlier stage of gestation might need a higher intensity stimulus than at 36 weeks onward. In those studies, they used stimulation in the form of five pulses for 2 s producing 1500 cycles/s with a sound pressure of 125 dB, while the stimulus in the current study was 3 s of 30–80 Hz at 110 dB.

The second positive finding in the current study is that frequencies of only blinking and startle movements increased significantly after VAS, while other behaviors did not show any significant change. An explanation for this phenomenon is that blinking is related to central dopamine system maturation, which occurs at about 36 weeks of gestation [17]. Therefore, more frequent blinking was observed after VAS in the group aged 36–40 weeks. Moreover, blinking was documented to be related to startle as being a part of the blinking startle reflex response to stimuli [40], and the circuits of blink reflex and startle reaction share some criteria as both are modulated by prepulse inhibition [41]. Therefore, this might explain the concurrence of significant increases in both of these parameters together after 36 weeks of gestation.

In conclusion, fetal responses to VAS showed an increase in blinking and startle movement after 36 weeks of gestation, which might represent an advanced stage of fetal brain and CNS maturation and response to external stimulation. Further studies with different intensity stimuli are needed to detect earlier stages of fetal neurodevelopmental maturation, and to allow accurate comparison between studies, because most of the available neurobehavioral studies using VAS were done long time ago and tremendous differences in the resolution and technical abilities which happened should be taken into consideration during comparison of the results of the current study and previous ones.

Limitations of this study included small sample size and discrepancy in the number of the subjects of 36–40 weeks compared with other age groups, which occurred due to difficulties in obtaining clear views especially in earlier gestational ages. Such number differences may influence the results. Moreover, although VAS is widely used in fetal surveillance and well-being, there is a lack of controlled trials addressing the safe limits of frequency and duration of its application. Standardized guidelines should be elicited to ensure the safe use of VAS in both clinical and research aspects. Finally, 4D ultrasound assessment of fetal response to VAS might become a novel, simple technique for the evaluation of fetal well-being in future clinical practice. Its use provides precise observation of fetal facial expressions and fetal movements both the spontaneous ones and those occurring in response to stimuli like VAS. This might directly indicate the different stages of developmental maturation of the fetal brain and CNS occurring during the intrauterine period.

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