

学 位 論 文

4D ultrasound study of fetal
facial expressions in the third
trimester of pregnancy

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4D ultrasound study of fetal facial expressions in the third trimester of pregnancy

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Conflict of interest

The authors declare no conflict of interest.

Abstract

Objective: To evaluate the frequencies of fetal facial expressions in the third trimester of pregnancy, when fetal brain maturation and development are progressing in normal healthy fetuses.

Methods: Four-dimensional (4D) ultrasound was used to examine the facial expressions of 111 healthy fetuses between 30 and 40 weeks of gestation. The frequencies of 7 facial expressions (mouthing, yawning, smiling, tongue expulsion, scowling, sucking, and blinking) during 15-minute recordings were assessed. The fetuses were further divided into three gestational age groups (25 fetuses at 30-31 weeks, 43 at 32-35 weeks and 43 at ≥ 36 weeks). Comparison of facial expressions among the three gestational age groups was performed to determine their changes with advancing gestation.

Results: Mouthing was the most frequent facial expression at 30-40 weeks of gestation, followed by blinking. Both facial expressions were significantly more frequent than other expressions ($p < 0.05$). The frequency of yawning decreased with the gestational age after 30 weeks of gestation ($p = 0.031$). Other facial expressions did not change between 30 and 40 weeks. The frequency of yawning at 30-31 weeks was significantly higher than that at 36-40 weeks ($p < 0.05$). There were no significant differences in other facial expressions among the three gestational age groups.

Conclusions: Our results suggest that 4D ultrasound assessment of fetal facial expressions may be a useful modality for evaluating fetal brain maturation and development. The decreasing frequency of fetal yawning after 30 weeks of gestation may explain the emergence of distinct states of arousal.

Keywords: 4D ultrasound, fetal behavior, fetal facial expression, fetal neurophysiology, fetal neurodevelopment

Introduction

Fetal brain development starts as early as in the 7th week of gestation [1]. A series of brain developmental changes takes place throughout pregnancy [2]. In the first and second trimesters, anatomical changes are the hallmark [3, 4], and therefore can be directly assessed by two-dimensional (2D) sonography [5].

On the other hand, functional brain developmental changes predominate over anatomical changes in the third trimester of pregnancy [6]. Functional connections between the cerebral cortex and peripheral nervous system appear at 28 weeks of gestation, as indicated by evoked potentials [7]. The upper motor control system (cerebral hemispheres, and basal ganglia) becomes mature at 34 weeks of pregnancy [8]. Development of the six-layered lamination of the neocortex takes place after 32 weeks, as a result of neural differentiation and the laminar distribution of thalamocortical axons [9]. The third trimester is also characterized by brain stem maturation with a distinguished sleep–wakefulness pattern due to pontine maturation [10].

Facial expressions are not separate from central nervous system (CNS) developmental changes. They start to be observed at 10-11 weeks of gestation [3]. Changes in their frequencies occur through gestation [11]. Eye movement patterns become more complex in the third trimester, due to mid-brain maturation. At 36-38 weeks, eye movements become linked with the fetal heart rate [12, 13].

These changes in the frequencies of facial expression, and their link with other body functions represent a crucial part of a set of behavioral states [14]. Previous neurodevelopmental study concluded that these behavioral

states develop due to the functional development of the fetal CNS [15]. Moreover, it is well documented that fetal behavior represented by fetal movements and facial expressions reflect well-being of the fetal brain and CNS [16-19]. Therefore, the evaluation of facial expressions, especially in the third trimester of pregnancy, might represent a direct method to assess developmental changes of the fetal brain and CNS. The change in frequencies of these expressions at that stage might reflect maturity of brain areas controlling these facial expressions.

There have been numerous studies on four-dimensional (4D) ultrasound assessment of fetal facial expressions [20-29]. However, the number of subjects studied in the third trimester of pregnancy, especially after 36 weeks of gestation, was very small. Because of the small amounts of amniotic fluid relative to the fetal size, and the difficulty in obtaining an ideal sagittal view of the fetal face depending on the fetal position, there are limitations regarding 4D ultrasound studies of fetal facial expressions.

The current study focuses on 4D ultrasound evaluation of fetal facial expressions in the third trimester as an indicator of brain development at this critical stage, which is believed to represent maturational stage of the fetal brain and CNS functions [30].

Materials and Methods

The study was conducted during a two-year period from April 2014 to April 2016. Pregnant Japanese women, who were at 30 to 40 weeks' gestation and scheduled to undergo routine ultrasound examinations, were asked to

participate in a 15-minute examination of fetal facial expressions. Only healthy non-smokers with singleton pregnancies were included in the study. Data about the smoking history were obtained from a questionnaire filled in by each pregnant woman during the first antenatal visit. Pregnancies of high maternal or fetal risk (multiple pregnancy, pregnancy-induced hypertension, gestational diabetes, intrauterine growth restriction, threatened preterm labor, polyhydramnios, and chromosomal abnormalities) were not enrolled. Maternal risk factors were excluded based on examination and data present in the maternal antenatal record. The gestational age was calculated from the first day of the last menstrual period, and confirmed by the first-trimester or early second-trimester 2D sonographic examinations.

The fetuses were considered normal based on a 2D sonographic mid-trimester anomaly scan according to the guidelines of the International Society of Obstetrics and Gynecology [31]. Fetal growth was assessed using Japanese growth charts [32]. All pregnancies were only examined once. Examinations were performed using Voluson E8 (GE Healthcare, Milwaukee, WI, USA) with a curved array transabdominal transducer (4-8.5 MHz). To obtain an ideal view in order to assess fetal facial expressions, the transducer was arranged so that sagittal sections of the fetal face—including the forehead, nose, and mouth—were always obtained. The crystal array of the transducer was automatically passed over the region of interest 40 times per second (maximum speed), and the resultant 4D images were shown on a monitor. All examinations lasted 15 minutes, and were recorded on a 4-gigabyte USB flash drive connected to the ultrasound machine. A quiet, temperature-controlled room was used for the examinations, which were

conducted mostly in the morning. No mechanical or acoustic stimulation was used during acquisition of the images. All examinations and data analysis were performed by one experienced examiner (M.A.M.A.).

The study was conducted following approval by the ethics committee of Kagawa University Graduate School of Medicine. All participants provided informed consent after a full explanation of the study objectives. One hundred and sixteen pregnant women participated in the study. Five cases were excluded (one case because the recording time was shorter than 15 minutes, and four cases due to inability to obtain their delivery data because deliveries were in other hospitals). One hundred and eleven were eligible to be included in the study. They were divided into three gestational age groups: the first group included 25 pregnancies between 30-31 weeks of gestation (17 at 30 weeks, and 8 at 31 weeks), the second group was from 32-35 weeks of gestation (7, 11, 9, 16 at 32, 33, 34, and 35 weeks), and the third group was from 36-40 weeks (13, 18, 6, 5 and 1 at 36, 37, 38, 39, and 40 weeks). Clinical characteristics of the subjects in each group are shown in Table 1. Seven types of facial expressions were assessed: mouthing, yawning, blinking, tongue expulsion, sucking, scowling (grimace), and smiling. Mouthing was defined as a sequence of rhythmic movements involving the jaws, and could be associated with tongue movement. They could last from 1 to 15 seconds. Yawning represented prolonged wide and slow jaw opening followed by quick closure with simultaneous head retroflexion. Blinking was a reflex characterized by rapid closure and opening of the eyes, occurring involuntarily or as a protective mechanism. Tongue expulsion was protrusion of the tongue during mouth opening. Sucking involved a series of opening and

closing of the jaws, possibly associated with sinking of the cheeks towards the oral cavity. The fetus might suckle one of his/her fingers, toes, or the umbilical cord. Scowling was described as wrinkling of the bilaterally contracted eyebrows and the muscles between them with a simultaneous drop of the mouth angles bilaterally and curling of one of the lips. Smiling involved bilateral elevation of the mouth angles.

The results on the frequency of fetal expressions are shown as median and range values. Differences in the maternal age, birth age, birth weight, and umbilical artery pH were assessed by the analysis of variance. The sex ratio among the three gestational age groups was compared using the chi-square test. Differences in Apgar scores were investigated with the Kruskal–Wallis 1-way analysis of variance. The frequencies of the facial expressions at 30-31, 32-35 and 36-40 weeks of gestation as well as the frequencies of each facial expression among 30-31, 32-35, and 36–40 weeks were compared using the Kruskal–Wallis 1-way analysis of variance by ranks and multiple comparisons. The correlation between the gestational age and the frequency of each of the seven facial expressions was assessed using Spearman’s rank correlation coefficient. Statistical analysis was conducted with IBM SPSS statistical software, version 22 for Windows (IBM SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered to be significant.

Results

When comparing clinical characteristics among 30-31, 32-35, and 36-40 weeks, there were no significant differences in the maternal age, parity,

gestational age at birth, birth weight, sex, or Apgar score between the groups (Table 1).

In the 111 fetuses at 30-40 weeks of gestation, mouthing was the most frequent facial expression (median, 4; range, 0-23) followed by blinking (median, 3; range, 0-19). Frequencies of mouthing and blinking were significantly higher than those of smiling (median, 1; range, 0-6), yawning (median, 0; range, 0-5), tongue expulsion (median, 0; range, 0-4), scowling (median, 0; range, 0-4), and sucking (median, 0, range 0-7) (Fig. 1).

Yawning was the only facial expression to demonstrate a significant decrease in frequency with advancing gestation ($p < 0.05$) (Fig. 2), although the correlation coefficient for yawning and increasing gestational age was low ($r = 0.184$). The other six facial expressions did not show a significant change in frequency with gestational age.

Mouthing and blinking remained the most frequent expressions in the 30-31-week group (Fig. 3), 32-35-week group (Fig. 4), as well as during 36-40 weeks (Fig. 5). Comparing facial expressions among 30-31, 32-35, and 36-40 weeks demonstrated that yawning was significantly less frequent at 36-40 weeks of gestation compared with at 31-32 weeks (Fig. 6). Other facial expressions did not demonstrate any significant differences among the three gestational age groups.

Discussion

In our previous studies on 4D ultrasound evaluations of fetal facial expressions at 20-34 weeks of gestation, mouthing was the sole most

frequent facial expression [26, 33, 34]. Kurjak et al. [23] reported that blinking and mouthing movements are dominant between 30 and 33 weeks of gestation. However, there has been no 4D ultrasound study on the patterns of the frequency of fetal facial expressions late in the third trimester. In the present study, mouthing and blinking were the most frequent facial expressions at 30-31, 32-35, 36-40, and 30-40 weeks of gestation, respectively. After approximately 30 weeks of gestation, there is an increase in long-duration fetal movements, referred to as epochs and episodes, and the neurobehavioral regulation of fetal movements is crucial during this period [35]. Horimoto et al. [30] found that the concurrence of regular mouthing with the non-rapid eye movement period after 35 to 36 weeks' gestation suggests the maturation of fetal brain functioning seen in the newborn. Brain functions also regulate the rate of spontaneous eye blinking [36, 37], and an increase in the spontaneous eye blinking rate is thought to be related to central dopamine system maturation [38-41]. These results suggest that the concurrence of mouthing movement and eye blinking may be related to the maturation of fetal brain development after 30 weeks of gestation.

It was reported that there is no change in the frequency of fetal yawning assessed by 2D sonography between 20 and 36 weeks of gestation [42]. In this study using 4D ultrasound, yawning showed a decreased frequency with advancing gestation in the third trimester of pregnancy, coinciding with the results obtained with 4D ultrasound by Reissland et al. [43], as well as Kurjak et al. [23]. Yawning is concerned with the arousal process of the brain [44]. With advancing gestation, the rhythmic control of sleep and wake times becomes more established. This results in frequent waking

episodes and less of a need for yawning as a stimulus for brain arousal. 'Yawning indicates a harmonious progress in the development of both the brainstem and the peripheral neuromuscular function, testifying to the induction of an ultradian rhythm of vigilance' [45]. Giganti et al. [44] also demonstrated a decreased frequency of yawning in preterm and near-term infants with the advancement of age. Therefore, the period of approximately 30 weeks of gestation might represent the emergence of distinct states of fetal brain arousal, as indicated by the significant decrease in the frequency of yawning. However, the low correlation coefficient for yawning and increasing gestational age as well as the overlapping ranges of numbers of yawning episodes among the three gestational age groups might indicate that the emergence of distinct states of fetal brain arousal after 30 weeks is very slowly progressing.

Reissland et al. [46] speculated that the increased frequency of fetal scowling with advancing gestation might be an adaptive process, which is beneficial after birth. Fetal scowling may represent the fetal response to pain [46, 47]. In this study, its frequency did not change after 30 weeks of gestation. The somatosensory evoked potentials (translating pain processing in the somatosensory cortex) develop at 29 weeks [48], and this might indicate the constant frequency of scowling in the third trimester of pregnancy.

Sato et al. [33] showed that the frequency of fetal smiling increased with advancing gestation between 20 and 34 weeks of gestation. In the present study, the frequency of smiling did not change after 30 weeks of gestation. Fetal smiling may facilitate the development of facial muscles in utero, and

may enhance a positive parental attitude [49]. The development of smiling in utero may represent an adaptive process to postnatal life.

In this study, the frequency of fetal suckling remained unchanged between 30 and 40 weeks of gestation. Previous 4D ultrasound studies reported its constant frequency between 20 and 34 weeks [33], and the results reported by Yigiter and Kavak [25], and Reissland et al. [50] also confirmed the stable frequency of fetal lip puckering in the second half of pregnancy [39]. Intrauterine sucking lacks the real postnatal stimulus (breast or bottle). However, its stable frequency with gestation indicates its importance as an essential training step in preparation for postnatal feeding.

The frequency of tongue expulsion was found to be constant between 30 and 40 weeks of gestation in the present study. Kurjak et al. [23] also found that its frequency is constant after 28 weeks of gestation. This constant frequency may represent a maintenance state of tongue training as an essential preparatory step for its use in lactation, as well as speech functions in postnatal life.

Limitations of the present study may be the small sample size and the lack of two investigators assessing the movements independently and blindly to gestational age. Therefore, intra- and inter-observer reproducibility for 4D ultrasound assessment of fetal facial expressions should be investigated in further research. In this investigation, most of the examinations were performed in the morning with few cases in the afternoon. This cannot allow analysis of the difference in fetal activity based on time/timing of the examinations. Future studies involving a larger sample size are needed to investigate the reproducibility of 4D ultrasound assessment of fetal facial

expressions and the difference in fetal activity at the time/timing of the examination.

In conclusion, the present study provided the normal parameters of fetal facial expressions in the third trimester of pregnancy, and suggests the possible link between facial expressions and brain development at this stage, when the fetal brain reaches advanced stage of maturity. Therefore, the full realization of fetal facial expressions and fetal behavior in different stages of gestation might enable us to better understand the functional development of the fetal brain and CNS. The developmental changes of facial expressions can selectively indicate the maturation and development of different parts of the fetal brain and CNS.

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Conflict of Interest

The authors have no conflict of interest.

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Legends

Fig. 1

Comparison of the frequencies of facial expressions at 30-40 weeks of gestation.

Fig. 2

The frequency of yawning in relation to the gestational age.

Fig. 3

Comparison of the frequencies of facial expressions at 30-31 weeks of gestation.

Fig. 4

Comparison of the frequencies of facial expressions at 32-35 weeks of gestation.

Fig. 5

Comparison of the frequencies of facial expressions at 36-40 weeks of gestation.

Fig. 6

Comparison of the frequencies of each facial expression among 30-31, 32-35, and 36-40 weeks of gestation.

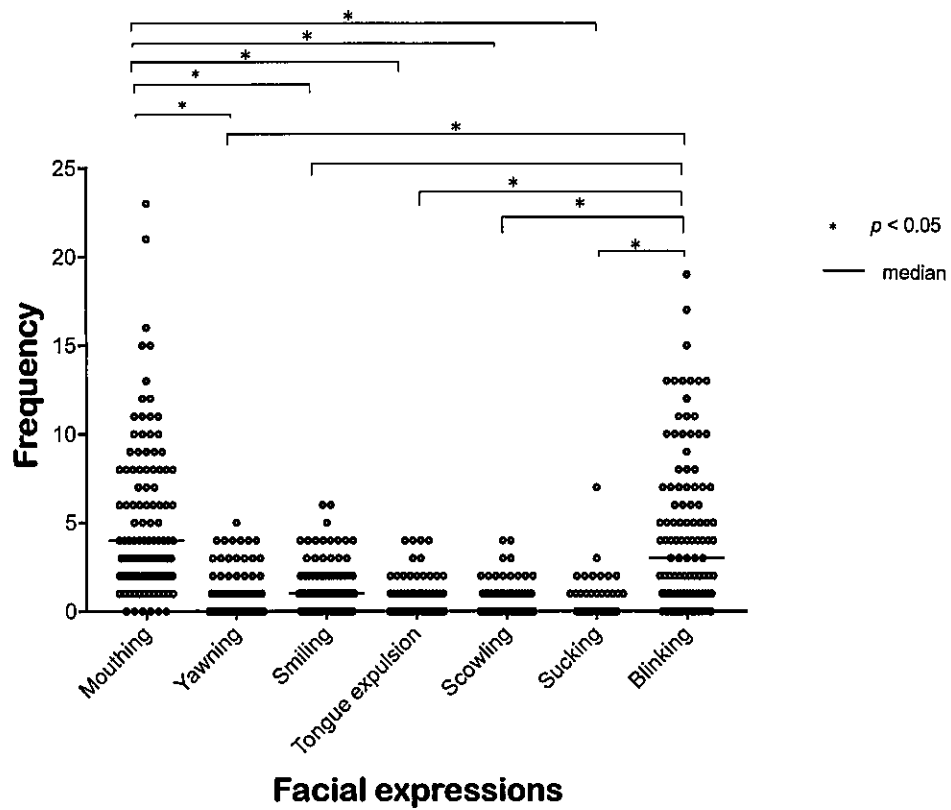


Fig. 1

Comparison of the frequencies of facial expressions at 30-40 weeks of gestation.

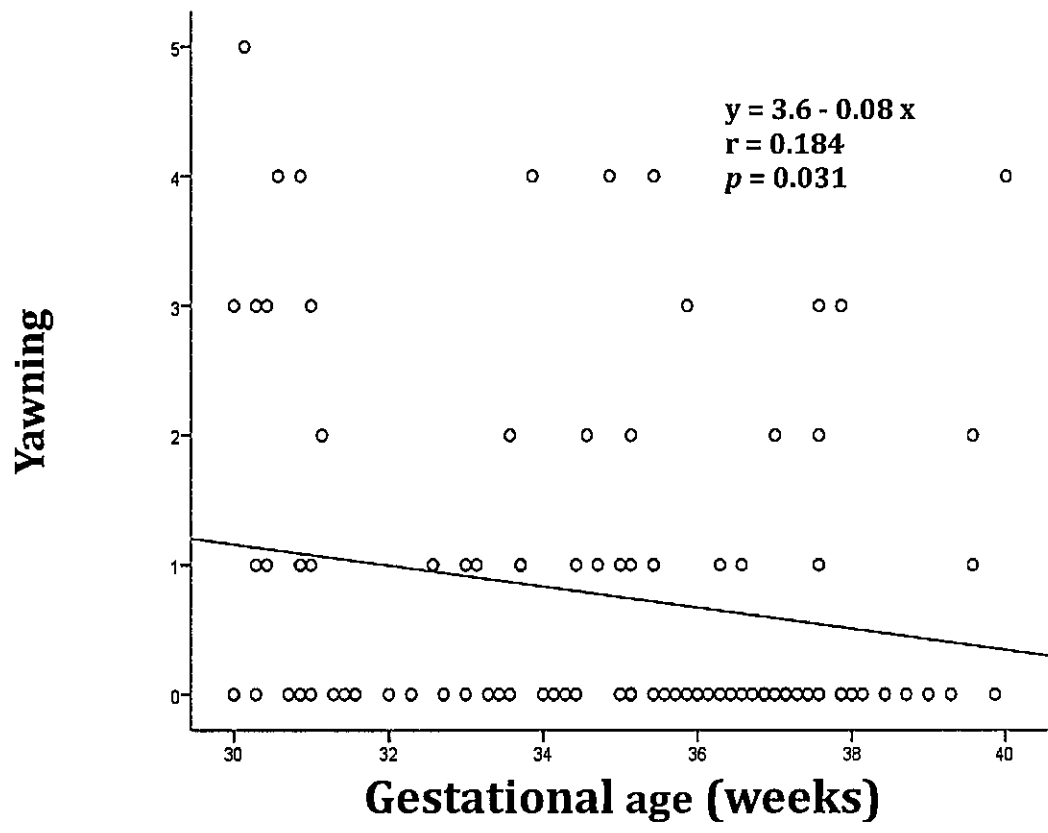


Fig. 2

The frequency of yawning in relation to the gestational age.

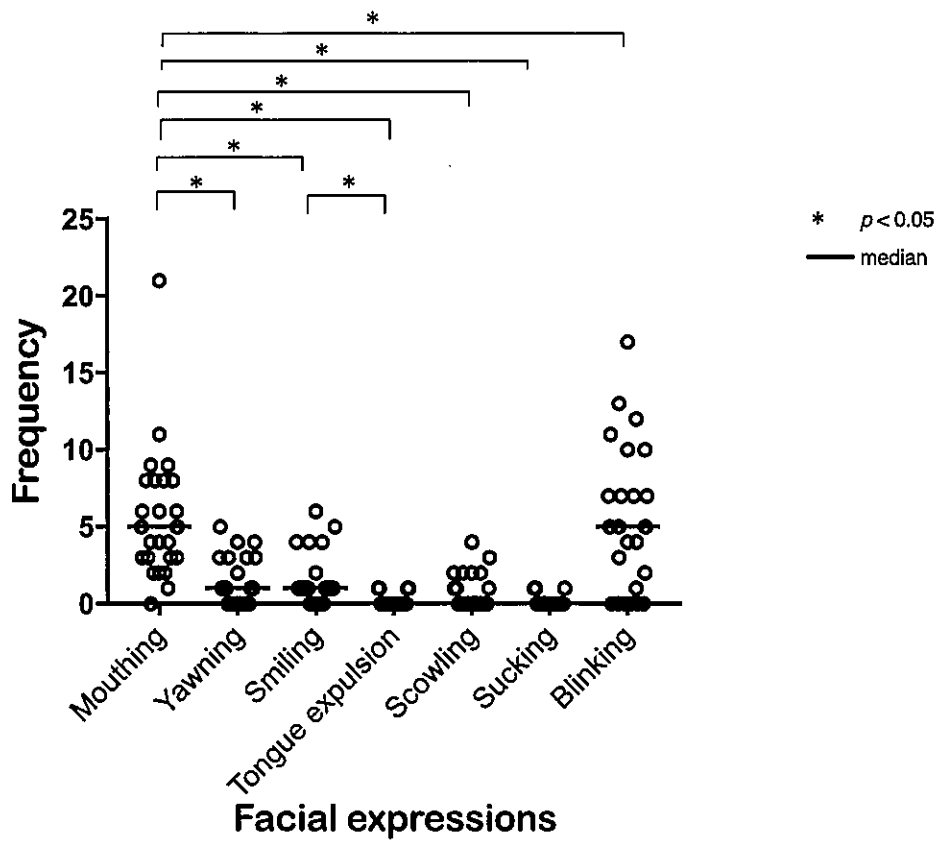


Fig. 3

Comparison of the frequencies of facial expressions at 30-31 weeks of gestation.

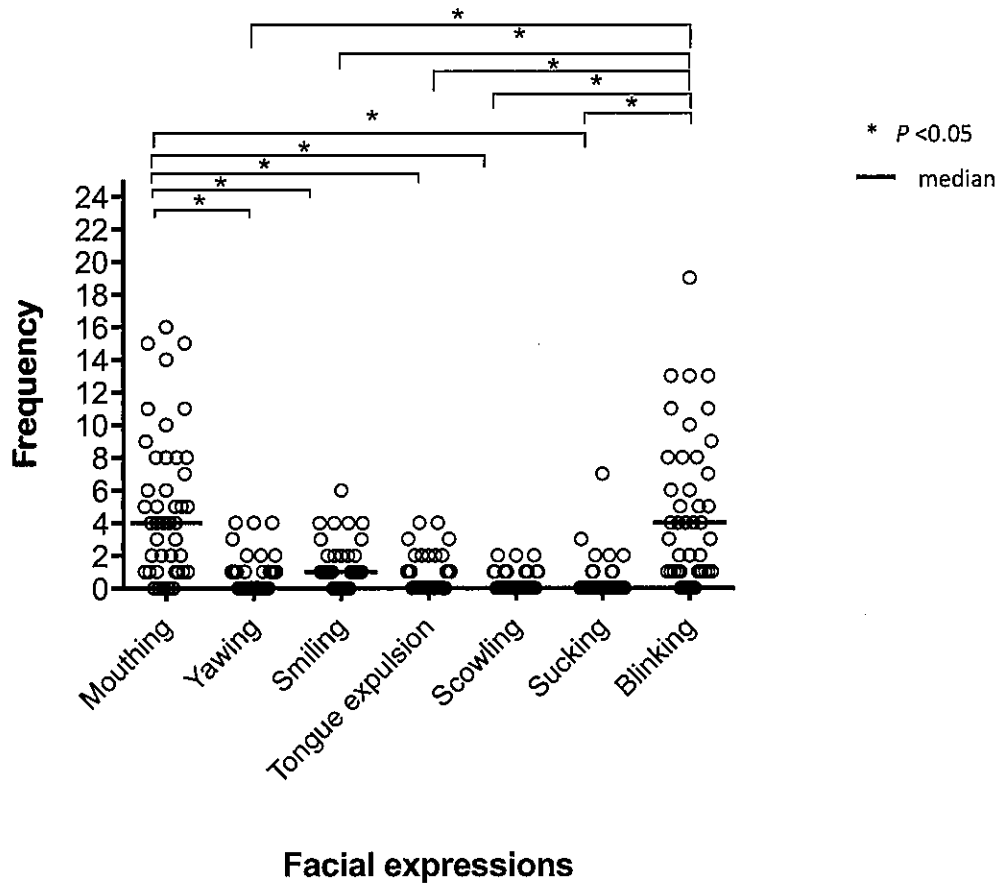


Fig. 4

Comparison of the frequencies of facial expressions at 32-35 weeks of gestation.

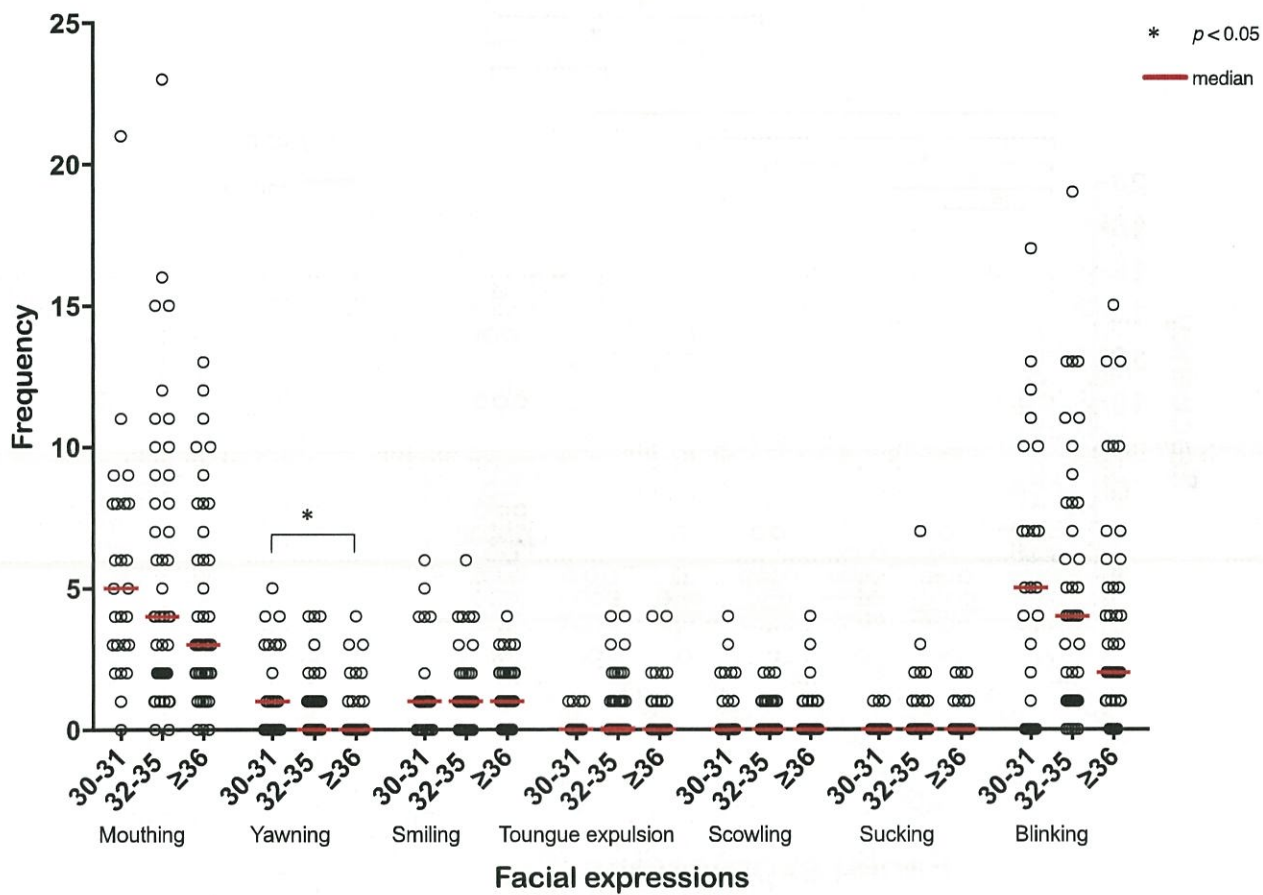


Fig. 6

Comparison of the frequencies of each facial expression among 30-31, 32-35, and 36-40 weeks of gestation.

Table 1 Clinical characteristics of subjects

Subject	n	Maternal age(y.o.)	Gestational age at birth(weeks)	Birth weight(g)	Sex (male /female)	Apgar score		UApH
						1 min	5min	
		Mean (SD)	Mean (SD)	Mean (SD)		Median (range)	Median (range)	Mean (SD)
30-31 weeks	25	31.2 (6.3)	39.7 (1.3)	3108 (391.5)	16/9	8 (5-9)	9 (7-10)	7.314 (0.044)
32-35 weeks	43	32.7 (5.2)	39.8 (0.4)	3121.4 (357.1)	20/23	8 (6-9)	9 (7-10)	7.293 (0.075)
≥ 36 weeks	43	32.6 (4.9)	39.6 (1.1)	3138.0 (366.7)	20/23	8 (5-9)	9 (6-10)	7.274 (0.082)
Significance	NS	NS	NS	NS	NS	NS	NS	NS

y.o., years old; SD, standard deviation; NS, not significant; UApH, umbilical artery blood pH.

Table 1 Clinical characteristic of subjects

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Dear Professor hata:

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Our referees have now considered your paper and have recommended publication in The Journal of Maternal-Fetal & Neonatal Medicine. We are pleased to accept your paper in its current form which will now be forwarded to the publisher for copy editing and typesetting.

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Thank you for your contribution to The Journal of Maternal-Fetal & Neonatal Medicine and we look forward to receiving further submissions from you.

Sincerely,
Professor Di Renzo
Editor in Chief, The Journal of Maternal-Fetal & Neonatal Medicine
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