

# Recent Topics in Fetal Behavioral Assessment

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## ABSTRACT

Many fetal behaviors are thought to indicate neurological development and may be useful for predicting neurodevelopmental outcomes after birth. In the present article, we review recent fetal behavioral studies focused on early spontaneous movements, eye movements (EMs), regular mouthing movements (RMMs), expression, and our own evaluation method of fetal brain dysfunction. Early spontaneous movement is one of the earliest expressions of neural activity. Changes in fetal EMs are thought to reflect the development of fetal sleep, while RMMs may reflect the development of non-rapid EM sleep. Fetal facial expressions, which may reflect higher brain function, can now be observed in more detail using four-dimensional ultrasound. Furthermore, we propose that assessing fetal brain function by combining multiple behavioral indicators may predict long-term neurodevelopmental outcomes after birth.

**Keywords:** Eye movement, Facial expression, Fetal behavior, Mouth movement, Neurodevelopment.

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## INTRODUCTION

Many fetal behaviors are thought to reflect central nervous system (CNS) development, and can therefore be used to predict neurodevelopmental outcomes after birth.<sup>1</sup> For the last 30 years, real-time ultrasound has allowed *in vivo* observation, and many studies have observed fetal behavior, with a particular focus on spontaneous movements, eye movements (EMs), and mouth movements in the fetus.<sup>2–4</sup> When four-dimensional (4D) ultrasound was introduced 15 years ago, many reports have addressed fetal facial expressions and postures, which are difficult to evaluate using two-dimensional (2D) ultrasound.<sup>5–7</sup>

In the present article, we summarize recent studies on early spontaneous movements, EMs, regular mouthing, fetal facial expressions, and our evaluation method of fetal brain dysfunction.

## SPONTANEOUS MOVEMENTS IN THE EARLY FETAL PERIOD

Fetal spontaneous movement is one of the earliest expressions of neural activity and has been well studied using ultrasound for many years. Fetal movements diversify rapidly in early pregnancy, and most movements that can be observed in term infants first occur by 16 weeks of gestation.<sup>3,8</sup> Fetal movements vary in frequency depending on the type, but most decrease slightly as pregnancy progresses.<sup>9,10</sup> In our previous study, in which we observed 62 fetuses at 8–20 weeks of gestation for 30 minutes, the total duration of fetal activity was longest at 15–16 weeks of gestation when measured without classifying fetal movements (unpublished data).

Four-dimensional ultrasound provided new perspective points on research. Ohmura et al. reported arm-hanging-like posture in fetuses between 10 and 20 weeks of gestation (Fig. 1).<sup>6</sup> This posture is peculiar to apes and is characterized by extension of both shoulders and elbows. According to the same study, the arm-hanging-like posture was most often observed at 14–16 weeks and then decreased. This posture seemed to correspond with subcortical nervous system development and decreased with the maturation of the vestibular spinal tract.

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Furthermore, 4D ultrasound made it possible to evaluate contact between twins in more detail than 2D ultrasound. Sasaki et al. reported that monochorionic diamniotic (MD) twins show more contact than dichorionic diamniotic (DD) twins at 10–11 weeks of gestation.<sup>11</sup> Further classifying the types of inter-twin contact revealed that the number of head-arm contacts between twins at 12 and 13 weeks of gestation differed between MD and DD twins.<sup>12</sup> Another study comparing singletons and twins between 12 weeks and 19 weeks of gestation reported that there were fewer spontaneous movements in twins than in singletons,<sup>13</sup> suggesting that neuromuscular development in twin fetuses may differ from that in singletons.

Although various studies have focused on fetal movement, there is insufficient knowledge about what kind of neural activity each fetal movement reflects, and no classification or evaluation methods have been developed. Accumulating the results of human fetus studies and comparing them to animal experiments will lead to a deeper understanding of spontaneous fetal movements.



Fig. 1: Ultrasound image of arm-hanging-like posture at 13 weeks of gestation. Reproduced from Ohmura et al.<sup>6</sup>

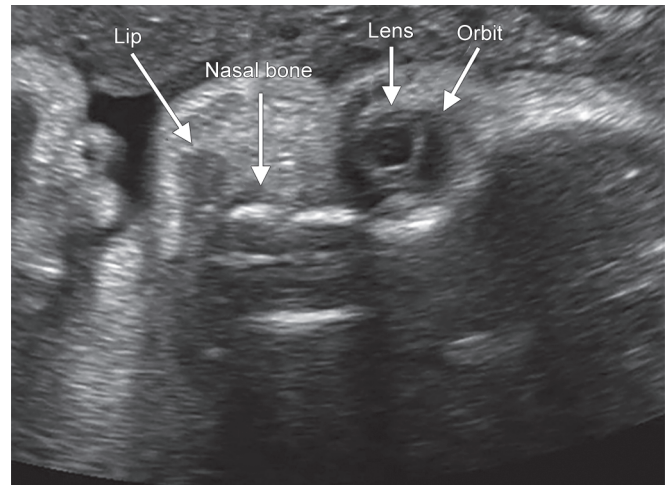


Fig. 2: Ultrasound image showing the investigation of fetal eye movement

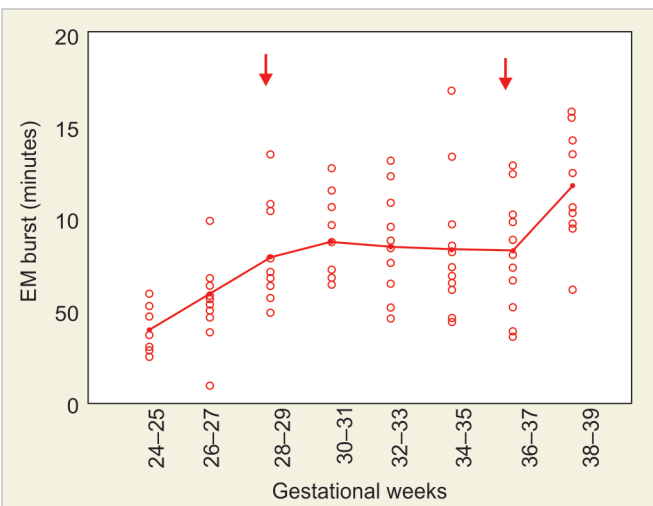
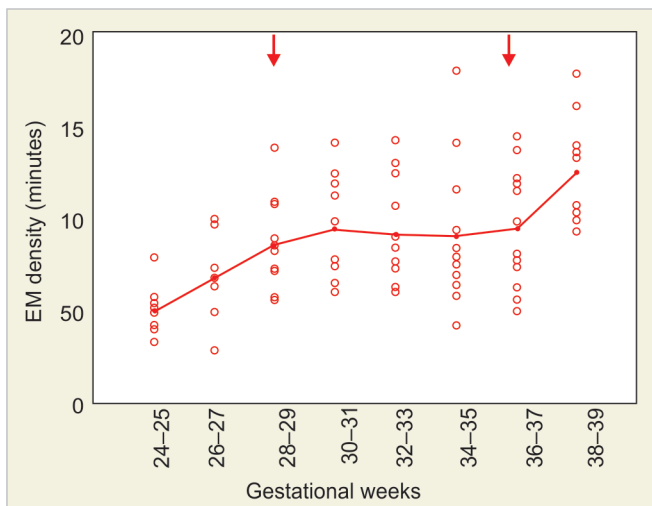


Fig. 3: Scattergram of eye movement (EM) density (left) and EM burst. The horizontal axis indicates gestational age in weeks, while the vertical axis indicates EM density (left) or EM burst (right). The solid line indicates the average of each group. The open arrows indicate the statistically defined inflection points. Reproduced from Okawa et al.<sup>18</sup>

### Eye Movements

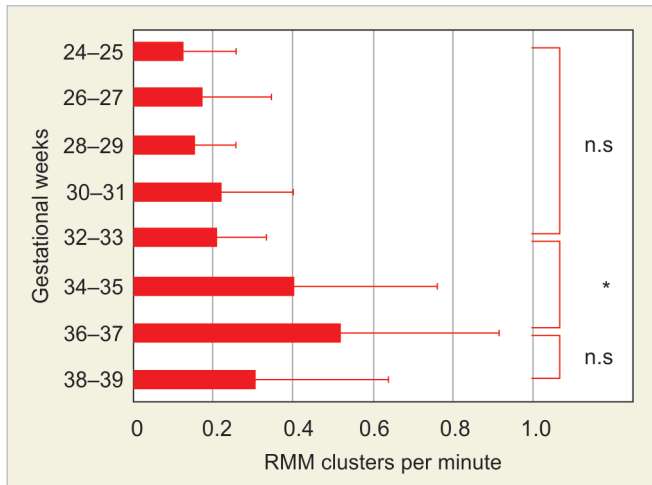
In one study, fetal EMs were evaluated from 14 weeks of gestation based on observation of the fetal lens (Fig. 2).<sup>14</sup> These movements start to consolidate at 24–26 weeks of gestation, and a distinction between EM and non-EM (NEM) periods becomes clear at 36–37 weeks.<sup>15</sup> The mean duration of EM periods increases from 29–30 weeks of gestation (7.2 minutes) to 37–38 weeks (28.1 minutes), and the mean duration of NEM periods increases from 31–32 weeks (5.9 minutes) to 37–38 weeks (23.0 minutes).<sup>16</sup> Therefore, one cycle of EM plus NEM period is thought to be 30 to 50 minutes in a term fetus.<sup>17</sup> To evaluate the quality of the EM periods, Okawa et al. reported changes in EM density and EM bursts, which are indicators of EM activity, at different gestational ages.<sup>18</sup> Specifically, EM density and EM bursts during each EM period increased until 28–29 weeks of gestation in a normal fetus. They were then constant until 36–37 weeks of gestation, and increased again after 38 weeks of gestation (Fig. 3).

Since fetal EM and NEM periods are considered the primordia of rapid EM (REM) and non-REM (NREM) sleep,<sup>19</sup> fetal EMs could be used to evaluate fetal sleep development. Rapid EM sleep is thought

to be important for neurodevelopment,<sup>20,21</sup> and one study involving preterm infants reported an association between REM activity and 6-month development postpartum.<sup>22</sup> To our knowledge, no reports have focused on the association between fetal sleep development and neurodevelopment after birth, so this association must be investigated further.

### Regular Mouthing Movements

Regular mouthing movements (RMMs) are frequent movements of the lips and lower jaw that can be observed *in utero* using ultrasonography.<sup>23</sup> They increase at 32–34 gestational weeks, and are concentrated during NEM periods after 35 gestational weeks.<sup>2</sup> Regular mouthing movements are often observed as clusters, and they increase in frequency between 32 and 37 gestational weeks (Fig. 4).<sup>24</sup> In full-term neonates, RMM clusters are associated with high-amplitude electroencephalograph waves during the NREM period.<sup>25</sup> Changes in RMMs and the development of RMM clusters may reflect the development of fetal sleep and the CNS. One study involving premature infants found that poor, non-nutritional



**Fig. 4:** Bar graph of regular mouthing movement (RMM) clusters per minute. The horizontal axis indicates the number of RMM clusters per minute, while the vertical axis indicates gestational age in weeks. The bars represent the mean and standard deviation. \* $p < 0.05$ ; ns, not significant; Reproduced from Maehara et al.<sup>24</sup>

sucking, which is similar to fetal RMMs, was associated with developmental problems.<sup>26</sup> As such, fetal RMMs may be a predictor of neural development after birth.

## FETAL FACIAL EXPRESSIONS

As mentioned above, eye and mouth movements have also been evaluated using 2D ultrasound. However, 4D ultrasound enables a more detailed classification of fetal facial expressions such as scowling and smiling.<sup>5</sup> Fetal facial movements may also reflect the functional development and maturation of CNS.<sup>27</sup> Kurjak's antenatal fetal neurodevelopment test (KANET), which takes into account facial expressions, has been proposed to evaluate fetal behavior.<sup>5,28,29</sup> The KANET is conducted on fetuses between 28 weeks and 38 weeks of gestation and evaluates the following eight items: isolated head anteflexion, cranial sutures and head circumference, isolated eye blinking, facial alteration or mouth opening, isolated leg movement, isolated hand or hand-to-face movements, finger movements, and gestalt perception of general movements.<sup>28</sup> The KANET score was reported to be consistent with postnatal neurodevelopmental assessment,<sup>30</sup> and abnormalities in the KANET score were associated with anatomical neurological abnormalities, cerebral palsy, and chromosomal abnormalities.<sup>31-34</sup> The KANET scores may also be associated with neurodevelopmental outcomes in early infancy.<sup>35</sup> Specifically, of 353 fetuses who were subjected to the KANET *in utero*, 337 were in the normal group, 16 were in the borderline group, and none were in the abnormal group. After a follow-up of  $\geq 2$  years, disabilities such as autism and developmental delay occurred in 1.48% of the children in the normal group (5/337) and in 18.75% of those in the borderline group (3/16), which was a significant difference. Although further investigation is needed, the KANET may predict neurodevelopmental abnormalities in infancy as well as in neonatal period.

## OUR EVALUATION METHOD OF FETAL BRAIN DYSFUNCTION

Several attempts have been made to design a prenatal screening system based on fetal behavior that can detect fetuses with CNS dysfunction in the general population.<sup>16,36,37</sup> In our previous study,

**Table 1:** Indicators for screening examination. Reproduced from Morokuma et al.<sup>38</sup>

1	Decrease or lack of fetal movement The mother reports feeling fewer than three fetal movements per 12-hours period or experiences complete cessation of fetal movement for the same duration
2	Persistent abnormal fetal heart rate pattern Abnormal fetal heart rate pattern is defined as a heart rate ranging from 120 to 160 bpm, with a decreased baseline variability of $\leq 5$ bpm and no acceleration in response to fetal movement Persistent abnormal fetal heart rate pattern is defined as an abnormal fetal heart rate pattern that continues for $\geq 120$ minutes
3	Congenital central nervous system malformations Central nervous system malformations that are diagnosable <i>in utero</i>
4	Polyhydramnios with unknown causes

we reported a two-step method for assessing fetal CNS function; we then evaluated the accuracy of this method for predicting postnatal CNS dysfunction.<sup>38</sup> The first step is a screening examination that takes into account the following four indicators: decreased or lack of fetal movements,<sup>39</sup> abnormal fetal heart rate,<sup>40,41</sup> congenital CNS malformations, and polyhydramnios with unknown cause (Table 1).<sup>37</sup> If the screening examination is positive, a brief ultrasound evaluation is performed as the second step. This examination is limited to five items to ensure that the ultrasound is quick; in our study, the median duration was 28 minutes (range: 11–60 minutes). The five indicators evaluated in the brief ultrasound evaluation are movements of the extremities, breathing movements, ultradian rhythm, REM period, and NREM period (Table 2). We defined poor neurological outcomes at 3 years of age as cerebral palsy, mental retardation, or developmental quotient of  $\leq 80$ .

Between January 2000 and December 2009, we evaluated 4,978 singleton fetuses born after 32 weeks of gestation at the Kyushu University Hospital. Ninety-three were positive in the screening examination. Among these, 25 (26.9%) had poor neurological outcomes. Among the 4,885 patients with negative screening results, 22 (0.5%) had poor neurological outcomes. Thus, the sensitivity and specificity of the screening examination for predicting poor neurological outcomes were 53% and 99%, respectively.

Among the 93 cases with positive screening results, 26 underwent the second examination. Of these, 10 had abnormal findings in the second examination, and 8 had poor neurological outcomes. In contrast, 14 of the 16 patients with normal findings in the second examination had good neurological outcomes. Thus, the sensitivity and specificity of the brief ultrasound evaluation for predicting poor neurological outcomes were 80% and 88%, respectively.

With additional testing and appropriate brief criteria, it may be possible to examine fetal brain development universally.

## CONCLUSION

In the present article, we reviewed recent studies of fetal behavior focused on early spontaneous movement, EMs, RMMs, fetal expression, and our evaluation method of fetal brain dysfunction.

**Table 2:** Indicators for “brief ultrasound evaluation”. Reproduced from Morokuma et al.<sup>38</sup>

1	Movement of extremities One episode of motion involving extension, flexion, external and internal rotation, or abduction and adduction of all four extremities during the observation period was considered normal
2	Breathing movement Breathing movement was considered normal if it continued for 30 seconds at least once during the observation period
3	Ultradian rhythm Alternation of eye movement and non-eye movement periods, which was considered normal when both periods were longer than 5 minutes
4	REM period Rapid EM (REM) and slow EM (SEM) patterns. REMs coexisting with SEMs were considered normal.
5	NREM period Concurrence of regular mouthing movement during the NEM period. One episode of regular mouthing during the NEM period was considered normal

Knowledge of fetal behavior is steadily accumulating, but there is still no widely used evaluation method based on this behavior, mainly because the developmental period and frequency of each fetal behavior, as well as its synchronization with other fetal movements, are very diverse and change as pregnancy progresses. We provided an overview of both the KANET and our evaluation method of fetal brain dysfunction, which may predict long-term neurodevelopmental outcomes as well as a short-term neural function after birth. Although further investigation is needed, it may be useful to combine multiple indicators to assess fetal neural function at appropriate gestational periods.

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