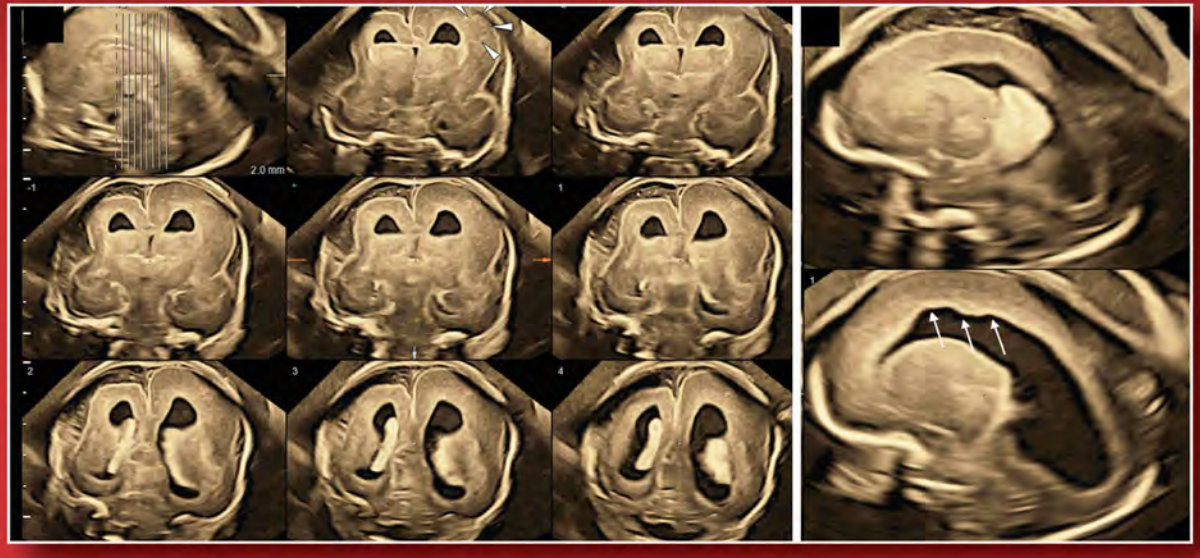
site www.jaypeebrothers.com, for detailed information on obstetrics & gynecology books, visit our website www.jaypeebrothers.com

Inter-University School of Medical Ultrasound
Ian Donald

Donald School

Fetal Brain Functioning



Asim Kurjak | *Foreword* **Frank A Chervenak**

JAYPEE

Contents

1. From Structure to Function: A Long Journey 1
Asim Kurjak, Milan Stanojević, Panagiotis Antsaklis
- Structural and Functional Development of Central Nervous System *1*
- Neonatal Aspect of Fetal Neurology *8*
- Postnatal Assessment of General Movements *10*
- Continuity of General Movements from Prenatal to Postnatal Life *11*
- Could Some Postnatal Signs of Neurological Disability be used Prenatally? *12*
- What is Kurjak's Antenatal Neurodevelopmental Test? *13*
- What have Studies about KANET Shown so Far? *17*

2. Morphological Approach to Cortical Formations 40
Ritsuko K Pooh
- Malformations of Cortical Development *42*
- Proliferation Disorders *43*
- Migration Disorders *46*
- Postmigrational Disorders *48*
- Future Perspective *50*

3. Fetal Cognitive Functions..... 53
Aida Salihagić Kadić, Asim Kurjak, Anja Šurina, Oliver Vasilj
- Fetal Neurodevelopment and Cognitive Functions *53*
- Prenatal Motor Development and Fetal Action *55*
- Prenatal Sensory Development and Fetal Perception of Stimuli *59*
- Learning and Memory in Fetal Life *61*
- Emotional Development of the Fetus *62*
- Fetal Stress and Cognitive Development *64*

4. Evolution of Assessment of Fetal Brain Function..... 71
Panagiotis Antsaklis, Maria Papamichail, Marianna Theodora, George Daskalakis, Asim Kurjak
- Fetal Central Nervous System: Stages of Development *71*
- Fetal Movements Evaluated by Ultrasonography *73*
- From Fetus to Neonate: The Progress of Neurobehavior *75*
- Introduction of Kurjak's Antenatal Neurodevelopmental Test *75*
- Review of Studies: 10 Years Experience of Kurjak's Antenatal Neurodevelopmental Test Application *78*

5. Brain Maturation and Development in Growth-restricted Fetuses: Functional Studies 89
Toshiyuki Hata, Riko Takayoshi, Aya Koyanagi, Yasunari Miyagi, Takahito Miyake
- Two-dimensional Sonographic Studies *89*
- Four-dimensional Ultrasound Studies *90*

6. Is Fetus and Neonate the Same Individual in Terms of Behavior? 95
Milan Stanojević, Asim Kurjak

- Epidemiology and Course of Neurodevelopmental Disability in Perinatal Period *95*
- Role of Neurological Clinical Assessment in Neonatal Period *97*
- Is Neuroimaging Important for Neonatal Neurological Assessment? *99*
- Why General Movements Count? *100*
- General Movements as a Predictor of Neurologic Disability in the Future: Lesson for Prenatal Assessment *101*
- Possibility of Longitudinal Assessment of General Movements from Prenatal to Postnatal Life *103*
- Prenatal use of Postnatal Signs of Neurological Assessment *104*
- Is Gravity Affecting Prenatal and Postnatal Motor Development? *105*
- Significance of Early Intervention and Other Procedures to Improve Neurodevelopmental Outcome in Children with Neurological Risk *106*
- New Published Data on the Continuity of Fetal to Neonatal Behavior *107*

7. Twin Fetal Behavior and Facial Expression: Four-dimensional Ultrasound Study 114
Toshiyuki Hata, Riko Takayoshi, Aya Koyanagi, Takahito Miyake

- Intertwin Contact and Intrapair Stimulation *114*
- Twin Fetal Movements before 20 Weeks *116*
- Twin Fetal Facial Expressions *117*

8. Fetal Awareness 120
Milan Stanojević, Asim Kurjak, Aida Salihagić Kadić, Lara Spalldi Barišić, Miro Jakovljević

- How Human Awareness can be Defined? *121*
- How Consciousness and Awareness are Developing? *121*
- Assessment of Brain Function *122*
- Possibilities of Four-dimensional Ultrasound in Assessment of Fetal Behavior *122*
- Importance of the Investigation of Fetal Self-awareness *127*

9. Neurosonogenetics 133
Ritsuko K Pooh

- Cranial Dysraphism (Neurulation Disorder) *133*
- Holoprosencephaly (Prosencephalic Disorder) *134*
- Agenesis of the Corpus Callosum *135*
- Malformations of Cortical Development *135*
- Proliferation and Apoptosis Disorders *137*
- Ventriculomegaly *139*
- In Utero Brain Injury and Damage *142*
- Future Perspective *145*

10. Assessment of Fetal Neurobehavior in Special Cases 152
Panagiotis Antsaklis, Maria Papamichail, Marianna Theodora, George Daskalakis, Asim Kurjak

- Ethnicity and Fetal Behavior *153*
- Fetal Sex and Fetal Behavior *157*
- Diabetes and Fetal Behavior *160*

- Hypothyroidism and Fetal Behavior *162*
- Psychotropic Drugs and Fetal Behavior *163*
- Fetal Response to Vibroacoustic Stimulation *163*
- Antenatal Corticosteroid Administration and Fetal Behavior *164*

11. Cognitive Functions in Pregnant Women 170
Natalia Lesiewska, Maciej Bieliński
- Brain Changes in Pregnant Women *170*
- Cognitive Functions in Hypertensive Diseases of Pregnancy *171*
- Gestational Diabetes Mellitus and Brain Function *175*
- Cognitive Functions and Obesity *179*
- Depressive Disorders and Cognitive Functions *181*

12. Kurjak's Antenatal Neurodevelopmental Test: Protocol for Evaluating Fetal Neurology In Utero 192
Panagiotis Antsaklis, Asim Kurjak
- From Fetal Movements to Fetal Neurobehavior *193*
- Kurjak's Antenatal Neurodevelopmental Test *194*

Index 213

CHAPTER 3

Fetal Cognitive Functions

Aida Salihagić Kadić, Asim Kurjak, Anja Šurina, Oliver Vasilj

INTRODUCTION

Our brain is fantastically designed to execute cognitive functions, such as perception, action, attention, learning, thinking, speaking, reasoning, remembering, problem solving, decision making, etc. The modern imaging methods, such as three-dimensional/four-dimensional ultrasound (3D/4D US) and functional magnetic resonance imaging (fMRI) have indicated that some of the cognitive functions are being born in fetal life.[1] This chapter serves as a review of fetal neurodevelopment, fetal sensory and motor development, intrauterine behavior and activities, and development of fetal cognitive functions. New data about fetal sensory perception, motor action, emotions, as well as fetal learning, memory, and consequences of fetal stress response on cognitive functions have been presented in this chapter.

FETAL NEURODEVELOPMENT AND COGNITIVE FUNCTIONS

Prenatal and postnatal sensory and motor experience contours the structure and function of the cerebral cortex. It has been well known that >99% of the human neocortex is formed prenatally, resulting in amazing diversity of fetal abilities, including cognitive functions.[1] The maturation of the cerebral cortex is a very complex and dynamic process influenced by intrinsic and extrinsic factors, stimuli, and the environment.[2] Brain development is also very dynamic and it relies on interaction of genetic, systemic, and experiential factors. To unlock the mystery of neurocognitive development, understanding of how brain systems emerge through the interaction of all of these factors is essential.[3]

The central nervous system (CNS) begins its development in an early embryonic period from the ectodermal germinative layer, and its differentiation and maturation continue postnatally. The neural plate is formed at the beginning of the 3rd week as a precursor of the future brain and the spinal cord. Lateral edges of the neural plate elevate to form the neural folds which merge in the midline and create the neural tube. Fusion begins in the cervical region and proceeds in cephalic and caudal directions. The open ends of the neural tube form the cranial and caudal neuropores. Final closure of the cranial neuropore occurs at the 24th day while closure of the caudal neuropore occurs a few days later, on the 28th day. The process of neural tube formation is called "primary neurulation". Around the 22nd day of the embryonic life the forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon) are distinguished in the rostral part of the neural tube as three primary brain vesicles. After the neural tube closes completely, cephalic flexure appears in the midbrain region and cervical flexure at the junction of the hindbrain and the

JAYPEE BROTHERS

spinal cord. Later on, the forebrain region is dividing into two parts: the diencephalon, characterized by outgrowing of the optic vesicles, and the telencephalon, basis for the future cerebral hemispheres. During the fetal life, the hemispheres continue to grow and develop into lobes, gyruses, and sulci. The rhombencephalon is the fundamental of the pons, cerebellum, and myelencephalon.[4] Caudal part of the neural tube, which is future spinal cord, develops in the process called "secondary neurulation".[5]

Histogenetic processes precede the growth of the neural tube and changes in shape and structure of its wall. Those are very complex overlapping processes divided into neurogenesis, migration, and cytodifferentiation. Production of neurons starts at the third gestational week (GW) with 125,000 and increases at the 7th week at a pace of 250,000/min.[6] Neurogenesis dominates in the embryonic and early fetal period, most intensively between the 8th and the 12th GW. Around the 20th GW neurogenesis is finished. Migration is accentuated in the middle of the gestation, from the 18th to the 24th GW, and cytodifferentiation at the end of the fetal period and postnatally. Migration finishes at the 38th GW. Synaptogenesis in the spinal cord begins at the 6/7th GW, it is very intensive in the middle of gestation, from the 8th to 18th GW and after the 24th GW. In the cortical plate, synaptogenesis starts at the 8th GW and it is most intensive after the 8th gestational month and it proceeds 2 years postnatally. It is important to note that by 20 weeks, the cortex has acquired its full complement of neurons. Cortical area differentiation begins between the 24th and the 34th GW and continues until the end of gestation.[7] Histologically, there are three zones of the neural tube. Those are ventricular, intermediary, and marginal zone. The telencephalon also has subventricular and subplate zone. Neurogenesis is placed in the ventricular and subventricular zone of the telencephalon. The cortical plate, brainstem, diencephalon, and basal ganglia nuclei, which are final targets of the neurons and the glial cells, are genetically predisposed. Transitional zones are being created during their migration, representing temporary forms of the cerebral cortex organization. Hence, during the embryonic and fetal period, the brain is formed not only of adult structures but also of transitional structures which are not found in the adult human brain.[8]

The subplate zone is considered as a key zone for the development of the cerebral cortex since it is a place where early synaptogenesis, a creation of temporary synapses of afferent axons and neurons, is carried out. It is formed between the 13th and the 15th week of gestation when a number of cortical synapses grow. A six-layered lamination of cerebral cortex appears after the 32nd GW, proceeding the process of neuronal differentiation and laminar allocation of the thalamocortical axons. This, however, does not represent the end of the cerebral cortex development since it continues intensively even after the birth, especially in the association regions of the cortex.[7,8] Although the neurons and the pathways are present already at the neonates, their quantitative and qualitative features and their connections still need fine tuning. Therefore, in the permanent interaction with environment, the development continues during the postnatal life. Between 8 months and 2 years of life postnatal synapse generation is the most intensive, and it antecedes the development of more advanced cognitive functions such as speech.[9]

Cognitive functions are mediated by specialized areas of neocortex distributed

JAYPEE BROTHERS

across the cerebral hemisphere. Large areas of association cortex, which develop gradually during the fetal life, contribute to the cognition in particular ways. At the term, association areas display low activity, whereas high activity can be detected by fMRI in primary cortical areas. It is important to point out that deficits in the complex interneuronal connections can presage cognitive impairments.[10]

White matter myelination is a complex and long-lasting process. The development of the myelin sheath provides synchronized communication across the neural systems responsible for higher order cognitive functioning.[11] One of the fundamental parts of cerebral white matter—the corpus callosum—is formed around the 20th GW. It represents the major interhemispheric commissure and integrates sensory, motor, cognitive, and emotional functions from both cerebral hemispheres. Abnormalities of the corpus callosum include agenesis, partial agenesis, and thickness variations: hypoplasia and hyperplasia. In a large number of conditions that interfere with early cerebral development, these malformations are diagnosed. Different learning and behavioral difficulties, as well as speech and language delays, cognitive and motor impairments, including cerebral palsy have been associated with an abnormal volume of the corpus callosum.[11,12] There is also a correlation between splenial structure of corpus callosum and language skills. Impairment of visuospatial skills, attention, and motor coordination are results of over- or underdevelopment of the splenium. Furthermore, reduced posterior callosal connections have been linked with impaired social skills, diminished processing speed during complex tasks, and impairments in the excitatory interhemispheric transfer. Correlating the prenatal corpus callosum abnormalities with the known functions of its structures enables progressing into a more meaningful understanding of the prenatal neurological development of the white matter and postnatal neurological outcomes.[12]

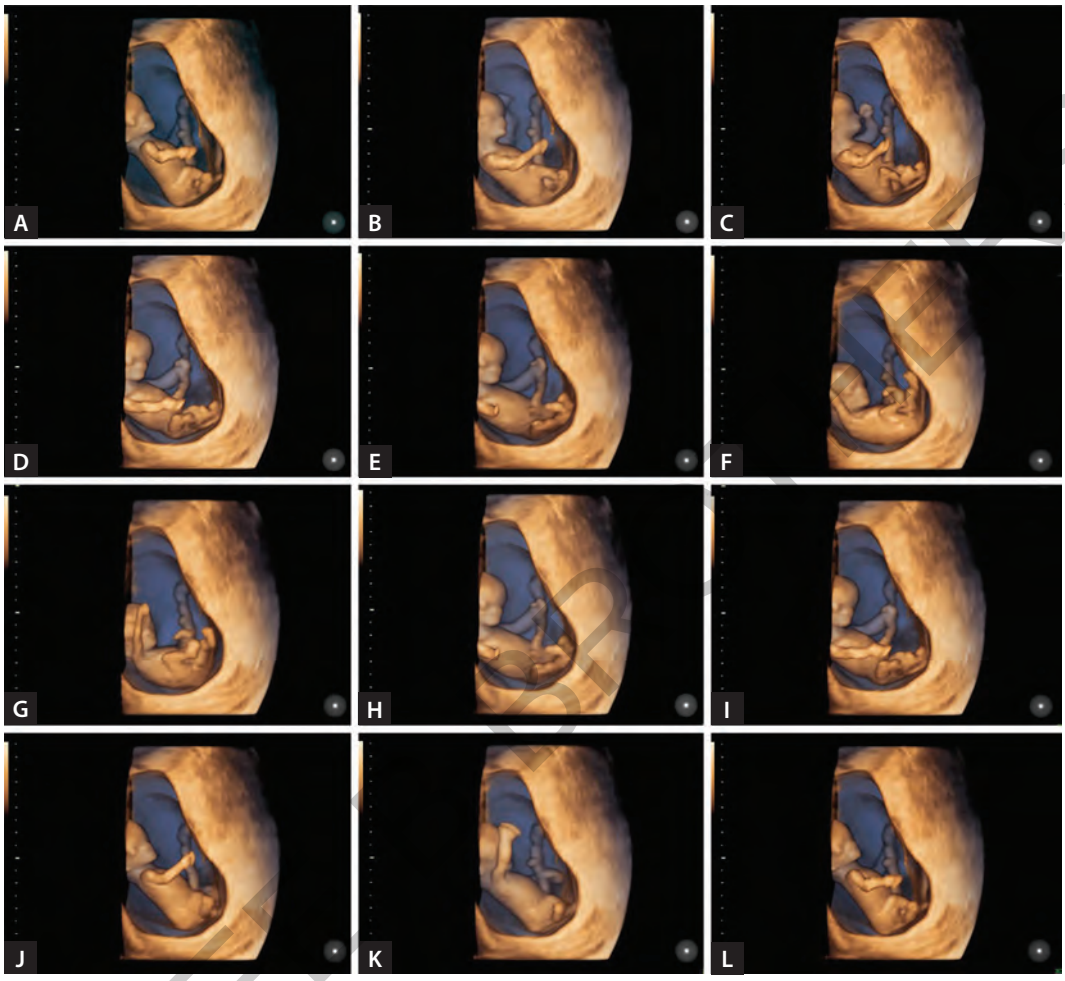
PRENATAL MOTOR DEVELOPMENT AND FETAL ACTION

With the CNS development, the repertoire of fetal activities and functions during pregnancy increases. Fetal behavior, which is a product of the functioning CNS, embodies all the activities of the fetus which can be observed or recorded by US or other imaging techniques. Fetal behavioral patterns and their variations during the gestational period match to the development and maturity of the fetal CNS. Aberrations from the normal fetal behavior in certain gestational period can refer to the presence of neurological disorders as well as other organ system abnormalities.[9]

The synapses, interneuronal connections, and innervated muscle fibers are prerequisites for fetal mobility which plays an important role in the development of the fetus. Between the 6th and the 7th GW the earliest synapses in the spinal cord are detected.[13] The first movements that can be seen are vermicular movements at 7–7.5 weeks, and they are a result of the neural activity of spinal motoneurons.[14] The earliest motor reflex activity appears simultaneously with the onset of spontaneous movements, indicating the existence of the first afferent-efferent circuits in the spinal cord.[15] General movements, which arise between the 8th and the 9th GW, are the earliest complex and well-organized movement pattern. Those movements include the head, trunk, and limbs **(Figs. 1A to L)** and express a supraspinal control on motor activity.[16,17]

The brainstem consisting of the medulla oblongata, pons, and midbrain is fashioned

JAYPEE BROTHERS



Figs. 1A to L: Series of three-dimensional ultrasonography (3D US) images of fetal general movements (11^{+1} weeks of gestation). The movements are of large amplitude and cause a shift in fetal position during this age period.

around 7th GW while by the end of the 8th GW the diencephalon and main parts of the cerebral hemispheres are formed.[18,19] Since the medulla matures earlier than other brainstem structures, activities under its control such as breathing-like movements, heart rate alternations, and reflexive movements of the head, trunk, and limbs appear prior to other functions. Around the 10–11th GW, facial movements, also controlled by cranial nerves V and VII, emerge.[18] Number, frequency, and diversity of fetal movements increase after 10 weeks. General movements, which used to be slow and of limited amplitude, become more pronounced.[20] From the 10th GW, when the fetus starts demonstrating signs of lateralized behavior, earliest signs of right- or left-"handedness" are present. Stimulation of the brain is known to influence the brain organization. It is considered that fetal motor activity may eventually stimulate the brain

JAYPEE BROTHERS

to develop lateralization of function.[10] From GW 13 onward, a "goal-orientation" of hand movements appears and a target point can be recognized for each hand movement.[21]

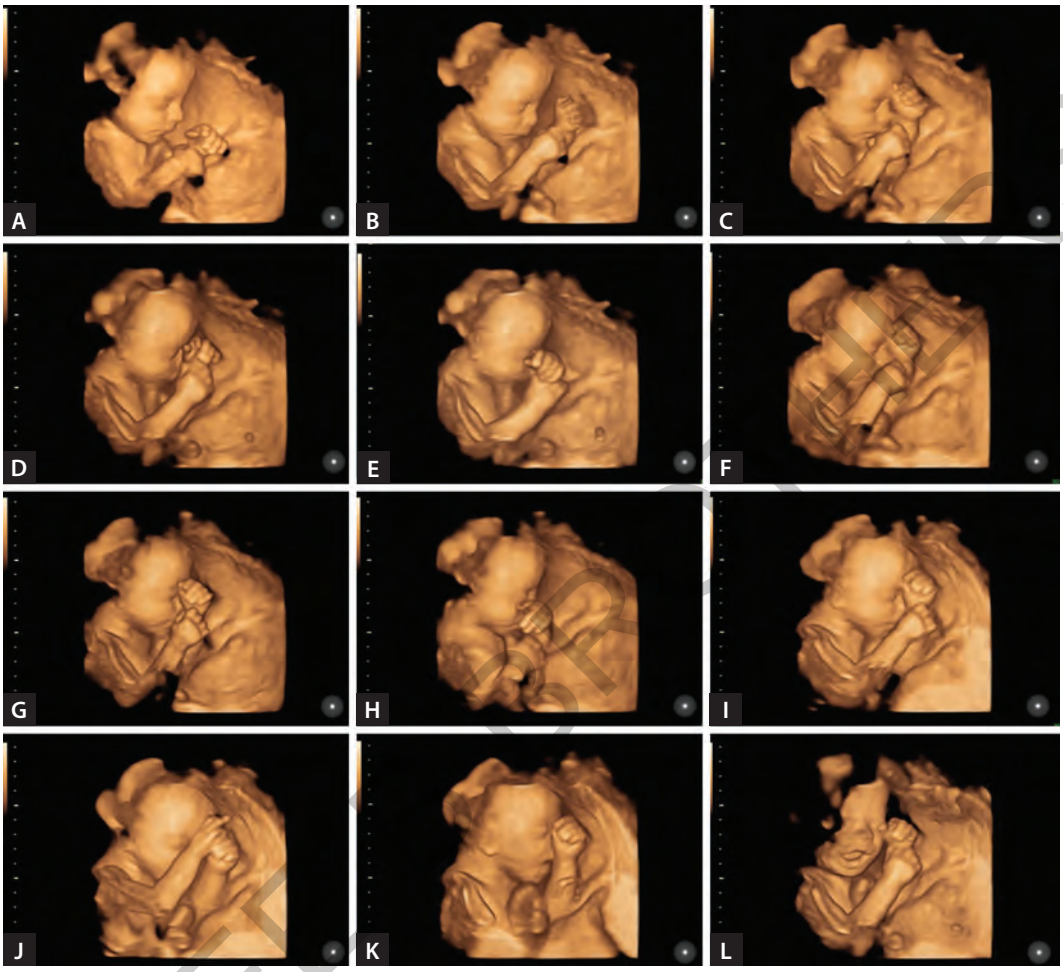
The most frequent movement pattern in the first trimester of pregnancy are general movements, which are always graceful in character.[22] These big **(see Figs. 1A to L)** and slow movements last from a few seconds to 1 minute. Their intensity, force, and velocity vary, and sequence of the head, neck, trunk, and extremities movements are undefined. Those characteristics are analyzed after the US recording when their qualitative aspects: complexity, variations, and fluency are being described. It appears that predictive value of general movements is important for detection of neurodevelopmental disorders, such as cerebral palsy.[23]

In the second trimester, fetal motor activity and fetal behavior are very diverse as a consequence of the development of neural connections, axons, synaptogenesis, and dendrite proliferation. Structures of the brainstem continue to mature, causing an increase in the complexity of fetal behavioral patterns and activities. Also, the second half of pregnancy is characterized by a gradual organization of fetal movement patterns.[9] The periods of fetal quiescence begin to increase, and the rest-activity cycles become recognizable. However, cerebral pathways are still not mature enough and the cerebral cortex cannot be considered responsible for motor activity and behavioral patterns.[7] On the other side, the brainstem gradually matures and starts to take over control of fetal movements and behavioral patterns.[18] During the second trimester a wide repertoire of fetal activity has been observed. This includes general movements, isolated movements of the extremities, head retroflexion, anteflexion, rotation as well as movements of the face, such as yawning, hiccupping, thumb sucking, swallowing, and mouthing.[16] Between the 16th and the 18th week, there appear sporadic eye movements as a result of the midbrain maturation. Structures important for eye movement control—cranial nerves III, IV, and V and medial longitudinal fasciculus—are situated in the midbrain.[18] 4D US imaging in the second and third trimester of pregnancy shows that fetuses change facial expressions like smiling, grimacing, and crying.[24] The fetal face reflects the brain development very well and it represents a diagnostic window for fetal diseases and syndromes.

It is fascinating that fetal movements serve not only to express different orientations, but also emotional states and manifestations of intentions.[25] Moreover, a kinematic study has revealed a presence of a recognizable form of intentional fetal hand movements which can be detected by 22 weeks of gestation, with kinematic patterns that depend on the goal of the action. This suggests that there is a surprisingly advanced level of fetal action planning.[26] Fetal hand movements toward the face, complex individual finger movements, and different facial movements in the second trimester are presented in **Figures 2A to L**.

In the third trimester of pregnancy, the CNS continues its development. The pons and mesencephalon proceed their developmental pathways. The spinothalamic tract ends it myelination at the 29th GW.[18] Regarding the motor development, there is a decrease in a number of fetal facial movements, general movements, and the head and arm movements. On the other hand, those movements become more and more complex.[9] Smaller volume of amniotic fluid, thus less space for the bigger fetus to move, was thought to be the reason for this decrease in fetal movement number. Now, we know that this is a consequence of the maturation

JAYPEE BROTHERS



Figs. 2A to L: Series of three-dimensional ultrasonography (3D US) images of fetal hand movements toward fetal face (the second trimester). The movements are complex with variety of rotations, extensions, and flexions. This figure also shows complex individual finger movements accompanied with fetal head movements and different facial expressions.

of the medulla oblongata and more stable intrinsic activity of the brainstem, which includes control of the spontaneous fetal movements. At the 28th GW, eye-blinking movement pattern is at its peak frequency, while more complex eye movement occurs between the 33rd and 38th GW. It is important to stress that until delivery, the subunits of the brainstem remain the main regulator of all fetal behavior patterns.[18] However, developmental trends in fetal motor patterns may indicate the establishment of control of more cranial brain structures.[1]

It is unclear whether infants remember the movements they produced in utero. However, it has been found that fetal experiences, for example, exposure to sounds and language, are remembered postnatally.[27] Nevertheless, fetal movements provide the brain with sensory input that spurs its development.[1]

JAYPEE BROTHERS

PRENATAL SENSORY DEVELOPMENT AND FETAL PERCEPTION OF STIMULI

Information enters the neural system by means of sensory receptors which register sensory stimuli, such as sound, light, touch, pain, cold, heat, etc. Sensory information from the somatic body segments enters into the spinal cord through the dorsal roots of spinal nerves. Then they travel up to the CNS through dorsal column of the medial lemniscus and anterolateral tract, the thalamus to the somatosensory part of the cerebral cortex.[28] The fetus is able to process tactile, vestibular, taste, olfactory, auditory, and visual sensations. When the thalamocortical connections are generated, which occur between the 24th and the 26th GW, sensory information can be processed at the cortical level.[8] A minimum level of consciousness emerges after the 25th GW.[29]

The first senses that develop in utero are touch and pain. The beginning of their development is at the 7th GW. Perioral region is touch-sensitive from the middle of the 7th GW. That is the time after which the fetus gives the earliest response to pain, a motor reflex, which can be induced in various ways. In the early phase of development, there is no perception or processing of the pain in the higher parts of the brain.[30] Studies on twin pregnancies were useful in research of the touch and pain. It was detected that after the 10th GW monochorionic twins react by moving when stimulated by touch. On the other side, dichorionic twins react to touch after the 12th GW.[31,32] All parts of the fetal body, with exception of the back and scalp, are sensitive to touch at the 14th GW.[33]

Fetal pain is a neural process and a sense having an important effect on the CNS development because of the possible long-term cognitive, emotional, and behavioral consequences.[34] The fetus responds to painful stimuli with a wide spectrum of reactions **(Table 1)**, which include the neuroendocrine answer, activation of hypothalamus-hypophysis-adrenal axis, and autonomic nervous system.[9] However, it is necessary to emphasize that these responses do not reach the cerebral cortex. The ability to sense pain requires developed neural pain system, from nociceptors to sensory areas in the cerebral cortex. The fetus has the necessary connections to sense pain after 24–26th GW.[8]

To prevent fetal pain during invasive intrauterine procedures, it is necessary to remember the knowledge about fetal pain and the effects of fetal stress response. It is still uncertain if the fetus is fully aware of the pain and if there is any memory of fetal pain.[35] The fetus cannot experience pain prior to reaching of connections from the periphery to the cortex. From about 25 weeks the cortical pain response has been recorded by near-infrared spectroscopy. Pain-like facial expressions have been observed in preterm infants after 25 weeks and these

TABLE 1: Fetal response to painful stimuli.

Weeks	*Response*
7, 5	Motor reflex
16–18	Increase in fetal cerebral blood flow
18–23	Elevation of noradrenaline, cortisol, and β-endorphin plasma levels
25	The cortical pain response
>25	Facial expressions are similar to those of adults experiencing pain
>28	Shifts in sleep/wake state Changes of the heart rate and blood oxygen saturation

Source: Modified according to Salihagić Kadić A et al.[9]

JAYPEE BROTHERS

infants are probably conscious of pain. On the other hand, there is an opinion that the fetus may not be conscious of pain even after the 25th GW due to high endogenous sedatory and analgesic substances.[1] The fetus incorporates subconsciously pain experience into neurological development and plasticity. It has been shown that fetuses during fetal surgery can respond with bradycardia. This might be useful to assess fetal pain in the future.[36,37] According to the latest results of investigations, the fetus should be provided with analgesics directly during surgical interventions, in addition to doses administered to the mother, proving that fetal pain is evident in the second half of the pregnancy. Drugs used for maternal analgesia cross the placenta only partially and safety guidelines are given for fetal direct analgesia.[38]

The intrauterine environment is not deprived of the light and sound. Furthermore, for the development of fetal visual and auditory system, auditory and light stimulations are necessary.[39] Postnatal stimulation is also very important since the development of the visual system lasts until the 8th month after delivery.[40]

Studies revealed the developmental processes of the eye and their timeline. Visual connections between the retina, lateral geniculate nucleus, and visual cortex begin its development in the midgestation. Between the 23rd and the 27th GW, the thalamic projections reach the visual cortex. After the 36th GW, the maturation of visual cortex can be registered by surface positive evoked potentials. The amplitude of visually evoked potentials can be used in the assessment of fetal habituation to light stimuli.[41] Fetal eye motility is very important in retinal (neuronal) cell differentiation and in the eye functional maturation.[42] Stimulative intrauterine environment, as well as postnatal environmental enrichments, fosters the development of the optic system on the molecular, physiological, and behavioral level.[40,43]

The fetus lives not only in stimulating matrix of the tactile and motor information, but also the acoustic stimuli. The fetus reacts to exogenous acoustic stimulation and as the pregnancy progresses, fetal response to these stimuli changes.[44] Between the 22nd and the 25th GW, the cochlear function is developed and its maturation continues in the first 6 months postnatally. Neural structures which are important for auditory system development are cochlear nuclei in the medulla oblongata and pons, auditory follicles in the mesencephalon, and primary auditory cortex. The pons and mesencephalon are later to mature in comparison with the structures of the medulla oblongata. For this reason the selective answer to sound and vibration arises later. The fetus responds to strong sound stimuli delivered to the maternal abdomen by reflexive rotation of the trunk, head, and with lateral eye movements. Fetal reactions to very loud sounds have been registered at 26 weeks while in the third trimester progressive development of hearing has been observed.[18] At around 33 weeks of gestation, there is a change in the processing of complex sounds, such as music. In the younger fetuses, the response is limited to the acoustic properties of music. On the other hand, in older fetuses it seems that attention plays a role.[45] By the end of gestation, due to tonotopic organization of cochlear nuclei and maturation of the brainstem, the fetus is capable to distinguish different sounds. Moreover, the existence of preference to mother's voice and other familiar voices has been proved. Repeated sound stimulus, or lack of it, forms neural

JAYPEE BROTHERS

networks and tracts in the medulla oblongata. After that, these structures selectively react to the same stimulus that formed them. This indicates that the brainstem already at that time possesses the activity connected with learning, and the brainstem nuclei and auditory pathways show synaptic plasticity and sensitivity to exogenous stimuli.[18] Neuroprocessing mechanisms of music during fetal and neonatal development seem to have an important role in neuroplasticity and neurodevelopment, as human neural processing of music involves a complex bilateral network of the cortical and subcortical areas and integrates several auditory, cognitive, sensory, motor, and emotional functions.[46,47] Therefore, music could be integrated in the neonatal intensive care units. Improvement of environment increases positive experiences for a neonate.[47]

There are some factors that are known to affect the development of the auditory system. These are smoking,[48] intrauterine growth restriction (IUGR),[49] and hypertension in pregnancy.[50] Further, neonates of mothers who suffer from speech and hearing impairments, interestingly, may have delayed development of the auditory system.[51]

LEARNING AND MEMORY IN FETAL LIFE

Fetal learning and memory have been assessed by habituation methods, classical conditioning, and exposure learning. The possibilities of fetal learning and memory are astonishing. It should be emphasized that memory acquired prenatally lasts longer than it was initially considered.[52]

Habituation is a decline in response following repetition of the same stimulus from the 22nd GW onward.[53] This phenomenon is one of the most well documented and fundamental forms of nervous system plasticity. A major role of habituation is to limit the utilization of attentional resources for stimuli that are no longer salient.[54] We can distinguish habituation from adaptation of receptor as it requires an immediate recovery of the response on presentation of a different stimulus as well as faster response decrement upon representation of the original stimulus.[55,56] In 1925, the first study of fetal habituation was reported. Subsequent studies showed that, if fetuses repeatedly stimulated with the same stimulus, it resulted in a decrement of their response,[57,58] which was assessed by fetal heart rate alternations or fetal movements.[59] It has been noticed that younger fetuses require more exposure to the stimulus than older ones to register developmental trends. We need to mention that the presence of maternal stress and depression can affect in a negative way fetal habituation. This can cause developmental delays linked to the impaired function of the cerebral cortex.[60]

Classical conditioning involves the pairing of two stimuli: a conditioned and an unconditioned stimulus. When conditioned stimulus is presented alone it does not elicit response, while unconditioned stimulus elicits one. After repeated paired exposure to these two stimuli, the conditioned stimulus also elicits a response named a "conditioned response". This method of fetal learning has been demonstrated in 32–39 weeks old fetuses.[61] However, it could also be demonstrated on anencephalic fetuses. In studies conducted on chimpanzees, it was shown that fetuses can learn and retain obtained information for at least 2 months after birth.[62]

Exposure learning is done in a way that the fetus, after a number of exposures, is re-exposed to a stimulus, and then this response is compared to the "unfamiliar" stimulus or

JAYPEE BROTHERS

to the response of an unexposed fetus to the same stimulus. Exposure learning confirmed that fetuses can hear and learn the voice of the mother before birth, and this gave insight to the fetal preference of the mother's voice over an unacquainted one as well as mother's voice in utero over her voice after delivery.[63] Selective fetal cortical processing for the mother's voice over an unfamiliar voice has been reported at 34 weeks of gestation.[64] The fetus is able to learn and remember familiar auditory stimuli and retain this information over the birth period.[65] Rudimentary capacity for retention of information exists very early, at 30 weeks of gestation, while prenatally acquired auditory memory can last even 6 weeks. The long-term auditory memory might have a role in the developmental psychobiology of attention and perception as well as early speech perception.[52]

Other aspects of fetal learning and memory have been investigated as well. The fetus is able to distinguish pleasant from an unpleasant taste of amniotic fluid, and it seems that sweet taste is preferred. Furthermore, during fetal life the preference for a certain food may be acquired.[66,67] The fetus also learns through smell. In preterm infants, behavioral responses to pleasant and unpleasant smells can be observed from about the 29th week.[68]

It might be that fetal learning and memory have a role in the development of maternal recognition, attachment, establishment of breastfeeding, social recognition, and language acquisition.[61,69] When the fetus starts discriminating different speeches in utero, the process of prenatal language acquiring may be possible.[63] There was a study performed on 93 pregnant women to assess fetal learning and memory, based on habituation to repeated vibroacoustic stimulation of fetuses of 30–38 weeks of gestational age. Fetal learning and short-term (10 min) memory is found at 30th GW. Also, there is evidence that at the 34th GW fetuses are able to store information and retrieve it 4 weeks later.[70]

The fetus can detect, respond as well as remember for a relatively long time the stimuli which it experienced during the prenatal period. Recent study has shown a remarkable experience-dependent plasticity in the primary auditory cortex even before the brain has reached full-term maturation. Namely, extremely premature infants exposed to maternal sounds had significantly larger auditory cortex compared with control infants receiving standard care.[71]

EMOTIONAL DEVELOPMENT OF THE FETUS

As mentioned before, fetal movements express not only different orientations but also emotional states.[25] Facial expressions are one of the external signs of emotion. It is possible that fetal facial movements demonstrate endogenously generated physiologic reflex patterns. Actually, smiling as well as crying can be induced by the brainstem stimulation even with complete forebrain transection or destruction.[18] A full range of different fetal facial expressions, similar to emotional facial expressions in children and adults, has been revealed during the second and the third trimester of pregnancy by the use of 4D US.[24,72,73] With the progress of pregnancy, fetal facial expressions become more complex **(Figs. 3A to O)** and some of them such as facial expressions of pain or distress, are considered to be an adaptive process which might be useful postnatally.[74] "Cry-face gestalt" or "laughter-face gestalt" appear in the third trimester. It might be beneficial for fetal and maternal communication and bonding in postnatal life, as well as for the regulation of

JAYPEE BROTHERS



Figs. 3A to O: Series of three-dimensional ultrasonography (3D US) images of complex fetal facial expressions ranging from grimacing, sad, happy, expression of pain, calm fetal face, angry fetal face, facial expression of surprise, yawning, and smiling (36–39 weeks of gestation).

parental care.[75] It has been suggested that the facial expressions and emotion-like behaviors represent some kind of fetal emotion and awareness.[73]

The limbic system, and the amygdala in particular, is responsible for the experience and the expression of emotions. It is known that the amygdala begins its development

JAYPEE BROTHERS

in early embryonic life while during the first postnatal year it reaches an advanced stage of maturity.[76] It has an important and significant role in the mediation of emotional memory, attention, arousal, and the experience of love, fear, pleasure, and joy. It contains facial recognition neurons which discern the emotional significance of different facial expressions. The evaluation of faces in social processing is an area of cognition specific to the amygdala.[76] The amygdala is vital in evaluating the biological relevance of sensory information and for initiating behavioral responses based on the initial assessment of the presented stimulus. Facial expressions represent biologically important visual stimuli, and the amygdala neurons are very responsive to them.[54]

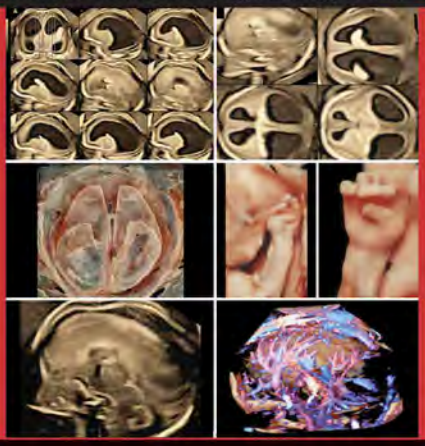
FETAL STRESS AND COGNITIVE DEVELOPMENT

Particularly important role in fetal growth and development has physiological condition in the intrauterine environment. It is necessary that the fetus is protected in an environment which gives optimal condition for growth and development. The stress has primarily protective role inducing different adaptations of the organism and allowing survival, however, fetal stress can have negative consequences on the structure and function of the organism, particularly the nervous system. There are several most important stressful factors which are: malnutrition of the mother, IUGR, fetal painful stimuli, and severe maternal emotional stress as well as stressful life events.[77]

Fetal hypothalamic-pituitary-adrenal response to stress is independent of mother's.[78] Moreover, it has been found that between the 18th and the 23rd GW the fetus secretes noradrenaline, cortisol, and beta-endorphin in response to painful stimuli **(see Table 1)**. Adaptation of the fetus to stress includes accelerated maturation, notably the maturation of the lungs and the brain. Unfortunately, even though this is a protective adaptation, interfering with the normal development of the CNS and other organ systems, it can leave long-term adverse sequels.[9,77] Cortisol, on one hand, initiates accelerated maturation of the brain and the lungs, but also, it has negative effects on growth of the fetal organism in a whole, as well as on the brain development. The hippocampus is the brain structure that contributes greatly to learning and memory. The hippocampus and parahippocampal region contain a large concentration of cortisol and the corticotropin-releasing hormone (CRH) receptors. Consequently, these regions are vulnerable to accelerated brain maturation, which can therefore cause different structural changes in the developing brain. Apart from structural changes, behavioral changes have been noticed as well. Stress-induced changes of the hippocampus include: decreased number of neurons and corticosteroid receptors, decreased level of serotonin, and decreased synaptic density on distinct hippocampal regions. These changes are later in life associated with memory impairment and learning disabilities. Hyperalertness and impaired fetal responsiveness to novel stimuli are behavioral changes associated with accelerated brain development. A cause of irritability and diminished attention may be fetal adrenocorticotropic hormone (ACTH) as well. Additionally, ACTH affects movement coordination and muscle tonus, which can be damaged due to great exposure to this hormone. Fetal CRH influences the timing of the birth, which means that the fetus has an active role in the initiation of the delivery. A high serum level of cortisol and CRH is

JAYPEE BROTHERS

detailed information on obstetrics & gynecology books, visit our website www.jaypeebrothers.com, for detailed information on obstetrics &



Donald School
Fetal Brain Functioning

Since Ian Donald began his pioneering studies of ultrasound examination of the fetal patient, the brain has always been the main focus of attention. After decades of studying, the many and varied aspects of brain morphology, thanks to advances in four-dimensional ultrasound, science has advanced to now permit an in-depth study of brain function during the perinatal period.

The book Fetal Brain Functioning addresses different aspects of assessment of fetal brain functions. It is highly recommended to sonologists and sonographers who will enjoy new insights in the beauty and precision of the function of the perinatal brain.



Asim Kurjak MD PhD is the Professor, Department of Obstetrics and Gynecology, Medical School University of Zagreb, Zagreb, Croatia. He is Professor Emeritus, University Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina. He has published 1,175 papers which have been cited more than 15,000 times (Google Scholar). He has authored, co-authored or co-edited 123 books. He is the President of International Academy of Perinatal Medicine; President of International Academy of Science and Art in Bosnia and Herzegovina; and the Director of Ian Donald Inter-University School of Medical Ultrasound. He has received doctorum honoris causa from Universities in Banja Luka, Budapest, Barcelona, Bucharest, Athens, Montevideo, Tomsk, Buenos Aires, St Petersburg, Moscow, Tirana and Khartoum.

Printed in India

Available at all medical bookstores
or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road,
Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
OBSTETRICS & GYNECOLOGY

ISBN 978-93-5465-646-0