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REVIEW ARTICLE

Fetal Cognitive Functions and 3D/4D Ultrasound

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ABSTRACT

In the past decades, advances in modern imaging methods, especially three-dimensional/four-dimensional ultrasound (3D/4D US), functional magnetic resonance imaging (fMRI) and fetal magnetoencephalography (fMEG), enabled the studies of the important neurodevelopmental events and opened the field of the investigation of fetal cognitive functions. Prenatal structural, functional and behavioral development, including the development of the central nervous system (CNS) and cognitive functional developments, are nowadays accessible to a better assessment due to the implementation of these methods. 3D/4D ultrasound imaging provides much important information about the fetus. It can detect various malformations and clarify suspicious findings, improve diagnostic accuracy, display fascinating fetal activity and also, it supports the advancements in fetal neurobehavioral and cognitive science. In this paper, a brief review of 3D/4D US assessed insights in the field of fetal neurodevelopment, particularly the development of fetal cognitive functions: sensory perception, motor action, emotions, learning, and memory, as well as the role of the fetal stress in cognitive development are discussed. Investigation of fetal cognitive functions is still in its beginning, but it is certain that future advances in the application of new imaging methods, such as different 3D/4D US modes and fMRI, will enable a better understanding of the cognitive abilities and functions of the fetus.

Keywords: Fetal behavior, Fetal cognitive function, Fetal stress, Four-dimensional ultrasonography.

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INTRODUCTION

In the past decades, advances in modern imaging methods, especially 3D/4D US, fMRI and fMEG, enabled the studies of the important neurodevelopmental events and opened the field of the investigation of fetal cognitive functions. Prenatal structural, functional and behavioral development, including the development of the CNS and cognitive functional development, are nowadays accessible to a better assessment due to the implementation of these methods.[1,2] 3D/4D ultrasound imaging provides much important information about the fetus. It can detect various malformations and clarify suspicious findings, improve diagnostic accuracy, display fascinating fetal activity and also, it supports the advancements in fetal neurobehavioral and cognitive science.[3] Apart from the US, fMRI and fMEG are also methods worth mentioning, as they offer an assessment of fetal brain function, notably the fetal response to the auditory and visual stimuli by fMRI, and the direct measurement of fetal neuronal activity by fMEG.[4]

Data on cognitive functions of the fetus could be important in clinical practice for the management of fetal pain, treatment of preterm infants and improvement of the neurological outcome of the fetuses from high-risk pregnancies. Furthermore, some of the cognitive deficits and impairments in childhood and adult age, like impaired learning and memory, deficits in attention, delayed language development, intellectual disability, may originate in the prenatal period.[1]

This paper will serve as a brief review of 3D/4D US assessed insights in the field of fetal neurodevelopment, particularly the development of fetal cognitive functions: sensory perception, motor action, emotions, learning, and memory, as well as the role of the fetal stress in cognitive development.

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STRUCTURAL AND FUNCTIONAL BRAIN DEVELOPMENT AND COGNITIVE FUNCTIONS

Prenatal and postnatal sensory and motor experience shapes and changes the structure and function of the cerebral cortex. Functional brain development begins *in utero* and more than 99% of the human neocortex is already formed prenatally, resulting in an amazing diversity of fetal abilities.[5] The maturation of the cerebral cortex is a very complex and dynamic process influenced by intrinsic and extrinsic factors, stimuli and the environment.[6] Contemporary models of brain development portray a dynamically developing system which relies on genetic, systemic, and experiential factors that interact in complex ways. An understanding of how brain systems emerge through the interaction of all of these factors is important to unlock the mystery of neurocognitive development.[7] In this section, neurodevelopmental processes and the emergence of cognitive functions will be described.

The CNS begins its development in an early embryonic period from the ectodermal germinative layer and its differentiation and maturation continue postnatally. The neural plate, thicked ectodermal layer, is formed at the beginning of the 3rd week as a precursor of the future brain and the spinal cord. The process of neural tube formation is called primary neurulation. The forebrain (prosencephalon), midbrain (mesencephalon) and hindbrain (rhombencephalon) are three dilations which are distinguished in the rostral part of the neural tube around the 22nd day of the embryonic life 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 spinal cord. Later on, the forebrain region divides into two parts: the diencephalon, characterized by outgrowing of the optic vesicles, and the telencephalon, basis for the future cerebral hemispheres. In the fetal period, the hemispheres continue to grow and develop into lobes, gyruses, and sulci. The rhombencephalon is the fundament of the pons, cerebellum, and myelencephalon.[8] Caudal part of the neural tube, future spinal cord, develops in the process called secondary neurulation.[9]

Histogenetic processes lead to the growth of the neural tube and changes in its wall's shape and structure. Those are very complex overlapping processes divided into neurogenesis, migration, and cytodifferentiation. Production of neurons starts at week 3 of gestation with 125,000 and increases at 7 weeks at a pace of 250,000 per minute.[10] It is important to note that by 20 weeks, the cortex has acquired its full complement of neurons. Between the 24th and 34th gestational week (GW), cortical area differentiation begins and continues until the end of gestation.[11]

Histologically, there are three zones of the neural tube: ventricular, intermediary and marginal zone. Besides these three zones, the telencephalon also has the subventricular and subplate zone. In the ventricular and subventricular zone of the telencephalon, all of the future neurons and glial cells are generated, that is, the neurogenesis is taking place in there. Final targets of the neurons and the glia cells: the cortical plate, brain stem, diencephalon, and basal ganglia nuclei, are genetically predisposed. During their migration, transitional zones are being created, 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.[12]

The subplate zone is a key zone for the development of the cerebral cortex because it is a place where early synaptogenesis, the creation of temporary synapses of afferent axons and neurons, is carried out. It is formed between the 15th and 17th weeks of gestation when a number of cortical synapses grow. Six-layered lamination of cerebral cortex appears after the 32nd GW, proceeding the process of neuronal differentiation and laminar allocation of the thalamocortical axons. However, this does not represent the end of cerebral cortex development. It continues intensively after the birth, especially in the association regions of the cortex.[11,13] In other words, even though the neurons and the pathways are present already at the neonates, their quantitative and qualitative features and their connections still need fine-tuning, so the development continues during the postnatal life in the permanent interaction with the environment. Postnatal synapse generation is the most intensive between 8 months and 2 years of life, and it antecedes the development of more advanced cognitive functions such as speech.[14]

Cognitive functions are mediated by specialized areas of neocortex. Large areas of association cortex, which develop gradually during the fetal life, are contained within each of the four lobes and contribute to the cognition.[15] Building up synapses in these regions enlarges its activity recorded by fMRI. This imaging technique, which enables investigation of fetal brain function, has shown low activity in the association regions of the neonate's brain in comparison with the adult brain. The highest activity was detected in the somatosensory, auditory and visual cortex of the newborn's brain.[16] A recent study has indicated that deficits in the complex interneural connections can presage cognitive impairments.[17] Functional MRI also enables examining functional connectivity development of the human fetus. It provides information about the spatial distribution and interaction of neural processing networks. By applying resting-state fMRI to the fetal brain, it is possible to noninvasively examine fetal functional brain circuits.[18] Resting-state studies in full-term[19] and preterm infants [20] have suggested the existence of a "proto", or partial, default mode network (DMN) in the early newborn. The DMN is an organized, baseline default mode of brain activation that is observed in adults and children.[21] Fetal resting-state fMRI examination offers the first opportunity to confirm the prenatal origins of this network and to evaluate processes by which it becomes organized before birth. Recent studies have shown that primitive forms of functional networks, including a primitive form of the DMN, appear to be present by mid-gestation.[18,22] *In utero* MRI has significantly increased our knowledge of early fetal brain development and has the potential of generating biomarkers for developmental prognosis in the future.[4]

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.[17] One of the substantial parts of cerebral white matter, the corpus callosum, is fashioned around the 20th GW. The corpus callosum integrates sensory, motor, cognitive and emotional functions from both cerebral hemispheres. It represents the major interhemispheric commissure. Abnormalities of the corpus callosum include agenesis, partial agenesis and thickness variations: hypoplasia and hyperplasia. These malformations are diagnosed in a large number of conditions that interfere with early cerebral development. An abnormal volume of the corpus callosum has been associated with different learning and behavioral difficulties, speech and language delays, cognitive and motor impairments, including cerebral palsy.[17,23] Moreover, there is a correlation between the splenial structure of corpus callosum with language skills. Over- or underdevelopment of the splenium results in the impairment of visuospatial skills, attention and motor coordination. Further, reduced posterior callosal connections have been associated with impaired social skills, diminished processing speed during complex tasks and impairments in the excitatory interhemispheric transfer.[24] 3D US enables a precise visualization of the normal (Fig. 1) and abnormal corpus callosum. By correlating the prenatal corpus callosum abnormalities with the known functions of its structures we are stepping forward into a more meaningful understanding of the prenatal neurological development of the white matter and postnatal neurological outcomes.[23]

PRENATAL NEUROMOTOR DEVELOPMENT AND FETAL INTENTIONAL MOVEMENTS

The repertoire of fetal activities and functions during pregnancy increases as the CNS develops. Understanding of fetal neuromotor development enables assessment of the fetal neural system integrity. Fetal behavior, a product of the functioning CNS, represents all the activities of the fetus which can be observed or recorded by ultrasound or other imaging techniques. Fetal behavioral patterns and its variations during the gestational period correspond to the development and maturity of the fetal CNS. Aberrations from the normal fetal behavior in a certain gestational period can refer to the presence of neurological disorders as well as other organ system abnormalities.[2,14]

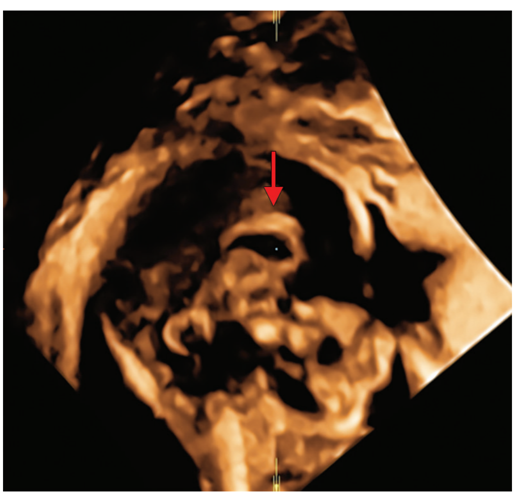

Fig. 1: 3D US image of the corpus callosum (displayed by an arrow; 19 + 6 weeks of gestation)

The synapses, interneuronal connections, and innervated muscle fibers are prerequisites for fetal mobility which is important for the development of the fetus. The earliest synapses in the spinal cord are detected between the 6th and 7th weeks of gestation.[25] The first movements that can be seen, vermicular movements at 7–7.5 weeks, are a result of the neural activity of spinal motoneurons.[26] Simultaneously with the onset of spontaneous movements, the earliest motor reflex activity appears, indicating the existence of the first afferent-efferent circuits in the spinal cord.[27] General movements (GMs), seen from the 8th to 9th weeks of gestation onwards, are the earliest complex and well-organized movement pattern. Those movements express a supraspinal control on motor activity and include the head, trunk, and limbs.[28,29]

It has been well known that neural cells begin to generate and propagate action potentials as soon as they interconnect. This intrinsic property of neurons explains recognizable temporal sequences of embryonic and fetal movements. What is more, studies have shown that neurons can communicate through the non-synaptic mechanism even before the onset of synaptogenesis.[14] The medulla oblongata, pons, and midbrain (the brainstem) develop around the 7th GW, while the diencephalon and main parts of the cerebral hemispheres are formed by the end of the 8th GW.[30,31] The medulla matures earlier than other brainstem structures, so activities under its control, breathing-like movements, heart rate alternations and reflexive movements of the head, trunk, and limbs appear before other functions. Facial movements, also controlled by cranial nerves V and VII, emerge around the 10th and 11th week.[30] After the 10th GW, number, frequency, and diversity of fetal movements increase. General movements, which used to be slow and of limited amplitude, become more pronounced.[32] The earliest signs of right- or left- 'handedness' are present from the 10th GW when the fetus starts demonstrating signs of lateralized behavior. Stimulation of the brain is known to influence the brain organization, and it is considered that fetal motor activity may eventually stimulate the brain to develop lateralization of function.[14] From gestational week 13 onwards, a 'goal-orientation' of hand movements appears, and a target point can be recognized for each hand movement.[33] Finally, at 13–14 weeks, isolated finger movements can be observed.[34]

General movements were found to be the most frequent movement pattern in the first trimester of normal pregnancies.[35] These movements are big and slow, lasting from a few seconds to one minute. Intensity, force, and velocity of these movements vary, and sequence of the head, neck, trunk and extremities movements is undefined. Those characteristics are analyzed after the US recording when their qualitative aspect: complexity, variations, and fluency are being described.[14] Gestalt perception, an overall assessment of GMs, is also a part of their analysis.[29,36] Predictive value of GMs appears to be important for detection of neurodevelopmental disorders, cerebral palsy for example.[37]

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 the pregnancy is characterized by a gradual organization of fetal movement patterns. The periods of fetal quiescence increase and the rest-activity cycles become recognizable.[2,14] However, cerebral pathways are still not mature enough and the cerebral cortex cannot be considered responsible for motor activity and behavioral patterns.[11] The brainstem, on the other side, gradually matures and begins to take over control of fetal movements and behavioral patterns.[30] Wide repertoire of fetal activity has been observed during the second trimester, including GMs, isolated movements of the extremities, retroflection, anteflexion, rotation of the head and facial movements like yawning, hiccuping, thumb sucking, swallowing and mouthing.[28] Between the 16th and 18th weeks, sporadic eye movements appear as a result of the midbrain maturation. In the midbrain, structures important for eye movement control: cranial nerves III, IV and V and medial longitudinal fasciculus are situated.[30] Further, 4D ultrasound imaging in the 2nd and 3rd trimesters of pregnancy shows that fetuses change facial expressions like smiling, grimacing and crying.[38] Recent data have indicated that fetal movements serve not only to express different orientations but also emotional states and manifestations of intentions.[39] The spatial and temporal characteristics of fetal movements are not uncoordinated or unpatterned. Furthermore, a kinematic study has shown a presence of a recognizable form of intentional fetal hand movements (Fig. 2) which can be detected by the 22 GW, with kinematic patterns that depend on the goal of the action. This suggests that there is a surprisingly advanced level of fetal motor planning.[40] It is important to stress that fetal motor behavior reflects the development of diverse cognitive, sensory and motor systems.A recent study has shown that primary sensorimotor and effective integration errors and poorly regulated motor intentions might underline autistic spectrum disorders.[41]

Fig. 2: Fetal hand to face movement, recorded by 3D/4D US (23 + 4 weeks of gestation)

The subplate zone, as already mentioned, is formed in the 2nd trimester and after this process, the first cortical electrical activity can be registered as a result of an increase in a number of cortical synapses.[12] Intensive synaptogenesis and establishment of the spinothalamic tract occur between the 15th and 20th GW but the myelinization of the spinothalamic tract continues until the 29th GW.[42] Studies conducted on monkey's and human's brain have shown that the thalamocortical connections develop between the 24th and 26th GW.[43,44] The cerebellum starts to mature at the 24th GW and the brain stem and cerebellum become accessible to clinical assessment around the 28th GW.[45]

In the 3rd trimester of pregnancy, the CNS continues its development. Regarding motor development, there is a decrease in the number of the GMs, and the head and the arm movements. On the other hand, these movements are becoming more and more complex. It was thought that the reason for this decrease in fetal movement number is a smaller volume of amniotic fluid, thus less space for the bigger fetus to move. Now we know that this is a consequence of the maturation of the medulla oblongata and more stable intrinsic activity of the brain stem which includes control of the spontaneous fetal movements. During the 3rd trimester, the frequeny of facial movement patterns shows a decreasing or stagnant developmental trend and the complexity of the fetal facial movements increases.[14] There is a possibility that these are consequences of the establishment of control of more cranial brain structures, not only of a maturation of the brainstem.[5,14] The fetal face reflects the brain development very well and that is the important reason for its investigation during the gestation. Ultrasonographic examination of the fetal face can also provide information that may lead to the diagnosis of anomalies in other organs or systems. Many genetic disorders affecting the CNS are characterized by dysmorphology and dysfunction of facial structures. Therefore, the fetal face represents a "diagnostic window" for fetal diseases and syndromes.[38]

From the beginning of the third trimester, evoked potentials can be registered from the cerebral cortex, indicating that the functional connection between the periphery and cortex operates from that time onwards.[46] At the 30th GW, by means of EEG, fetal sleep/awake patterns may be recorded, also as a result of the brain stem maturation.[47]

It is unclear whether infants might have a 'memory' for the movements they produced *in utero*. However, it has been found that fetal experiences, for example, exposure to sounds and language,[48-50] are remembered postnatally, so it might be possible that the infant also remembers prenatal movement patterns.[51] By all means, fetal movements provide the brain with sensory input that spurs its development.[1]

Fetal spontaneous movements, assessed by 4D ultrasound, are an important part of the Kurjak antenatal neurodevelopmental test (KANET)[52] which has proved its usefulness in prenatal assessment of the neurological outcome. This test has been used to asses almost 2000 fetuses and the results have indicated that KANET can recognize normal, borderline and abnormal behavior in fetuses from normal and pathological pregnancies.[53] Some of the studies that implemented this prenatal neurological scoring test have shown that fetuses with abnormal KANET demonstrate a deficiency in the repertoire of the movements, abnormal GMs, a fetal face like a mask or a neurological thumb (Fig. 3),[54,55] a sign of upper control motor system damage (the cerebral hemispheres and basal ganglia), which can indicate that the fetus suffered from severe hypoxia.[45] Comprehension of normal patterns of prenatal behavior is important as it is the foundation for differentiation of pathological aberrations which may be indicators of prenatal neurological impairment.[56]

Fig. 3: High definition 3D US image of fetal neurological thumb in a clenched fist (29 + 3 weeks of gestation)

PRENATAL NEUROSENSORY DEVELOPMENT AND FETAL PERCEPTION OF STIMULI

Information enters the neural system by means of sensory receptors which register sensory stimuli: sound, light, touch, pain, cold and heat. 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 the dorsal column of the medial lemniscus and anterolateral tract, the thalamus to the somatosensory part of the cerebral cortex. Vision, hearing and chemical senses are special sensory systems.[57] The fetus is able to process tactile, vestibular, taste, olfactory, auditory and visual sensations. When the thalamocortical connections are generated, tactile sensations can be processed at the cortical level. A minimum level of consciousness, by some studies, emerges after the 25th GW.[58] This section will provide a review of insights of fetal sensory perception with an emphasis on somatosensory, visual and auditory systems and the role of different sensory stimuli in the development of fetal cognitive functions.

Touch and pain are the first senses that develop *in utero*. Nociceptors are pain receptors, free nerve endings, present since 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. This motor reflex emerges in the middle of the 7th GW and it is controlled by the spinal cord. It resembles a withdrawal reflex but it is still very nonspecific. In this early phase of development, there is no perception or processing of the pain in the higher parts of the brain.[59] Further, from the middle of the 7th GW perioral region is touch-sensitive. The fetus reflexively moves his head in the opposite direction if this region is touched. Reflexive movements of the extremities in response to touch arise later. Upper extremities move if stimulated in the middle of the 10th GW, while lower extremities produce this response at the 14th GW.[14] Studies on twin pregnancies were useful in research of the touch and pain. It was detected that monochorionic twins react by moving when stimulated by touch after the 10th GW. Bichorionic twins, on the other side, react to touch after the 12th GW.[60,61] At the 14th GW, all parts of the fetal body, with exception of the back and scalp, are sensitive to touch.[62]

Fetal pain is a neural process and a sense. Taking into account its direct and permanent consequences, fetal pain has to be evaluated and explained in detail, considering different fetal answers to painful stimuli. Pain has an important effect on the CNS development, and it can leave long-term cognitive, emotional and behavioral consequences.[63] Fetal reaction to painful stimulus includes the neuroendocrine answer, activation of the hypothalamus-hypophysis axis and autonomic nervous system. However, it needs to be emphasized 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. Perception of sensory impulses is possible after they reach the somatosensory cortex around the 25th GW when the thalamocortical pathways and the cerebral cortex are connected.[12] Also, somatosensory-evoked potentials can be registered from the cortex at the 29th week of gestation. That is evidence of pain processing in the somatosensory cortex.[46] The way how the fetus reacts to pain was observed during invasive intrauterine procedures. During these procedures, in the 2nd trimester, between the 16th and 18th GW, cerebral blood flow increases.[64,65] Intrauterine transfusion through the innervated hepatic vein leads to an increase in plasma cortisol, noradrenaline and beta-endorphin levels in the fetus at the 23rd GW. On the other hand, there is no increase in levels of these hormones if the needle is inserted in the non-innervated umbilical cord.[66,67] Fetal pain is a very important issue especially considering the advances in intrauterine procedures and fetal surgery. It is necessary to take into account the knowledge about fetal pain and the effects of fetal stress response to prevent pain during invasive intrauterine procedures.[42] We are still uncertain if the fetus is fully aware of the pain and if is there any memory of fetal pain.[68] The cerebral cortex is necessary for pain perception, meaning the fetus cannot experience pain prior to reaching of connections from the periphery to the cortex. According to recent findings, the cortical pain response has been recorded by near-infrared spectroscopy from about 25 weeks of gestation. Preterm infants after 25 weeks of gestation are thus 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 sedative and analgesic substances.[16] Nowadays, it is considered that fetal adaptation to stress and stress hormone secretion, which can enormously change developmental processes and leave lifelong consequences, is probably a more dangerous and serious problem of the fetus than potential bad memories.[5,69]

Oftentimes, intrauterine life is described as living in darkness and silence but the intrauterine environment is not fully deprived of the light and sound. Moreover, auditory and light stimulations are necessary for the development of the fetal visual and auditory system.[70] Postnatal stimulation is also very important as the development of the visual system lasts until the 8th month after delivery.[71] Studies have revealed the developmental processes of the eye and their timeline. Visual connections between the retina, lateral geniculate nucleus and visual cortex begin their development in the midgestation. The thalamic projections reach the visual cortex between the 23rd and 27th GW. Maturation of the visual cortex can be registered by surface evoked potentials after the 36th GW. It has been shown that the amplitude of visually evoked potentials can be used in the assessment of fetal habituation to light stimuli.[72] Also, from the 28th GW onwards, a flash stimulus over the maternal abdomen can cause the visually evoked brain activity in the human fetus, recorded by magnetoencephalography.[73] Fetal eye motility is very important in retinal (neuronal) cell differentiation and the eye functional maturation.[74,75] Eye movements (Fig. 4) are, in addition to facial movements and expressions, an important indicator of healthy development because they can predict postnatal eye function.[75] Stimulative intrauterine environment, as well as postnatal environmental enrichments, foster the development of the visual system on the molecular, physiological and behavioral level.[76-78]

Besides the visual, tactile and motor stimuli, sound and vibration also affect neurodevelopment, in particular, the auditory system development. Studies have shown that the fetus reacts to exogenous acoustic stimulation and as the pregnancy progresses, fetal response to these stimuli changes.[79] These findings have opened many questions about fetal auditory system development. What is the connection between structural and functional development and what is the role of acoustic stimuli? The answer to these questions needs to be elaborated in studies of transmission of sound to the fetus, factors which influence fetal sound perception and fetal answer to acoustic stimuli.[80] The cochlear function develops between the 22nd and 25th GW and its maturation continues in the first six months postnatally. Neural structures important for auditory system development are cochlear

Fig. 4: High definition 3D US image of fetal face with opened eyelid (30 + 2 weeks of gestation)

nuclei in the medulla oblongata and pons, auditory follicles in 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 reacts to strong sound stimuli delivered to the maternal abdomen by reflexive rotation of the trunk, head, and with lateral eye movements. This response of the fetus to sound appears later in the gestation. Fetal reactions to very loud sounds have been detected at 26 weeks and progressive development of hearing has been observed in the 3rd trimester.[30] At around 33 weeks of gestation, there is a change in the processing of complex sounds, like music. In the younger fetuses, the response is limited to the acoustic properties of music. In older fetuses, on the other hand, it seems that attention plays a role.[81] Due to the tonotopic organization of cochlear nuclei and maturation of the brainstem, the fetus is capable of distinguishing different sounds by the end of gestation. Also, the existence of preference to the mother's voice and other familiar voices has been proved. Repeated sound stimulus, or lack of it, forms neural 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 brain stem nuclei and auditory pathways show synaptic plasticity and sensitivity to exogenous stimuli.[30] There are some factors that are known to affect the development of the auditory system and those are smoking,[82] intrauterine growth restriction (IUGR)[83] and hypertension in pregnancy.[84] Marshall et al. noted that neonates of mothers who suffer from speech and hearing impairments, interestingly, may have delayed development of the auditory system.[85]

FETAL LEARNING AND MEMORY

Studies of fetal cognitive functions are just at the beginning, but it is already found that the possibilities of fetal learning are astonishing. Furthermore, it has been shown that prenatally acquired memory lasts longer than it was initially considered.[86] Fetal learning and memory have been investigated by employing habituation methods, classical conditioning, and exposure learning.[1]

Habituation is a decrement in response following repetition of the same stimulus from the 22nd GW onwards.[87] 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.[88] Habituation can be distinguished from receptor adaptation 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.[89,90] The first study of fetal habituation was reported in 1925. Subsequent studies showed that repeated stimulation of fetuses with the same stimulus resulted in a decrement of their response,[91,92] which was assessed by fetal heart rate alternations[93] or fetal movements. It has been noticed that younger fetuses require more exposure to the stimulus than older ones to register developmental trends. It should be mentioned that fetal habituation can be affected in a negative way by the presence of maternal stress and depression. This can result in developmental delays linked to the impaired function of the cerebral cortex.[94]

Classical conditioning involves the pairing of two stimuli: a conditioned and an unconditioned stimulus. Conditioned stimulus does not elicit a response when presented alone, while unconditioned stimulus elicits one. After repeated paired exposure to these two stimuli, the conditioned stimulus also elicits a response-termed a 'conditioned response'. This method of fetal learning has been demonstrated in 32–39 weeks old fetuses.[95] However, it could also be demonstrated on anencephalic fetuses. Studies conducted on chimpanzees have shown that fetuses can learn and retain obtained information for at least two months after birth.[96]

Exposure learning is the third method used in the investigation of fetal memory and learning. It is used in such way where the fetus is re-exposed to a stimulus after a number of exposures and then this response is compared to the 'unfamiliar' stimulus or to the response of an unexposed fetus to the same stimulus. Exposure learning confirmed that fetuses can hear and learn mother's voice 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.[97] At 34 weeks of gestation, selective fetal cortical processing for the voice of the mother over an unfamiliar voice has been reported.[98] The fetus can learn and remember familiar auditory stimuli and retain this information over the birth period.[99] Rudimentary capacity for retention of information may be expressed very early, at 30 weeks of gestation, while prenatally, acquired auditory memory can last six-seven weeks. The long-term auditory memory might have a role in the developmental psychobiology of attention and perception as well as early speech perception.[86]

The fetus is able to distinguish pleasant from an unpleasant taste of amniotic fluid and it seems that sweet taste is the favorite taste even *in utero*.[5] The fetus can also learn different tastes and acquire taste preference as well as learn through smell.[16] Behavioral responses to pleasant and unpleasant smells can be recorded in preterm infants from about the 29th week. Furthermore, It has been shown that the preference for a certain food may be acquired during fetal life.[100]

Also, the process of prenatal language acquiring may be possible when the fetus starts discriminating different speeches *in utero*.[97,101] Presumably, fetal memory begins to develop prenatally. It probably functions in some rudimentary form and gradually develops as the fetus and child mature. Prenatal learning and memory may have a role in the development of maternal recognition, attachment, the establishment of breastfeeding, language acquisition and social recognition.[95] A study conducted 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, has shown that fetal learning and short-term (10 minutes) memory is present at 30th GW. Also, there is evidence that at the 34th GW fetuses can store information and retrieve it 4 weeks later.[102] The fetus can detect, respond, and remember for a relatively long time the stimuli experienced during the prenatal period. It is important to point out that recent investigation has shown experience-dependent plasticity in the primary auditory cortex before the brain has reached full-term maturation. Extremely premature infants exposed to maternal sounds had significantly larger auditory cortex compared with control infants receiving standard care.[103]

EMOTIONAL DEVELOPMENT OF THE FETUS

Emotions are being born in fetal life. Recent data reported on the ability of fetal movements to express different emotional states of the fetus.[39] Facial expressions represent one of the external signs of emotion. It is possible that facial movements demonstrate endogenously generated physiologic reflex patterns.[104] Smiling as well as crying can be induced by the brain stem stimulation even with complete forebrain transection or destruction.[30] Using 4D US during the 2nd and the 3rd trimesters of pregnancy has revealed a full range of different fetal facial expressions (Figs 5 and 6), similar to an adult's facial expressions.[38] As the pregnancy progresses, fetal facial expressions become more complex and some of them, like facial expressions of pain or distress, are considered to be an adaptive process useful postnatally.[51] High-resolution 4D scans allow us to study fetal facial features in detail, their development over the gestation.[38,105,106] and coordination of movements to form recognizable facial gestalts. 'Cry-face gestalt' or 'laughter-face gestalt' appear in the 3rd trimester. This might be beneficial for fetal and maternal communication and postnatal bonding.[107] In addition, it is assumed that facial expressions and emotion-like behaviors represent some fetal emotion and awareness.[108]

The limbic system, particularly the amygdala, is responsible for the experience and the expression of emotions.[109] The amygdala begins its development in early embryonic life[110] and has a great role in the mediation of emotional memory, attention, arousal and the experience of different emotions: 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.[109] The amygdala is essential for evaluating the biological relevance of sensory information and 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.[88] An interesting finding is that effective problems in girls, exposed to high levels of maternal cortisol in early pregnancy, are linked with larger amygdala volume measured by MRI.[111]

ROLE OF FETAL STRESS IN COGNITIVE DEVELOPMENT

Physiological conditions in the intrauterine environment have an extremely important role in fetal growth and development. The emphasis is on balance, which enables the fetus to develop in its full potential. The fetus has to be protected in an environment where there are no harmful stimuli and where optimal conditions for growth and development are conserved. Though the role of stress is

Fig. 5: Sequence of 4D HD live mode US images of fetal calm and satisfied face (31 + 2 weeks of gestation)

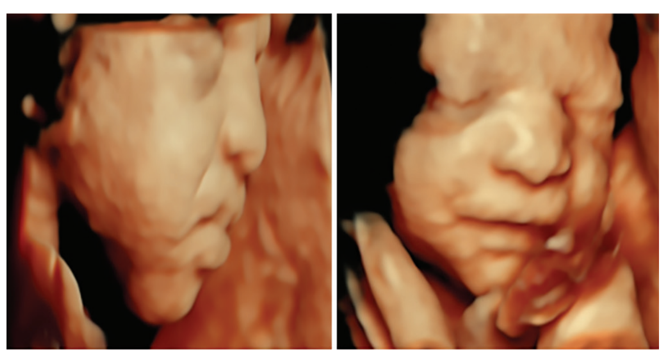

Fig. 6: Sequence of 4D HDlive mode US images of fetal face with dissatisfied and gloomy facial expression (30 + 22 weeks of gestation)

primarily protective, because it induces different adaptations of the organism and allows survival, fetal stress can leave negative consequences on the structure and function of the organism, especially the nervous system. The most important stressful factors are mother's malnutrition, IUGR, painful stimuli and severe emotional stress of the mother as well as stressful life events.[69]

Stressful response stimulates fetal neuroendocrine axis which is active since the midgestation. This includes the production and secretion of the corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol. Fetal hypothalamic-pituitary-adrenal response to stress is independent of the mother's.[112] In addition, it has been determined that the fetus secretes noradrenaline, cortisol, and beta-endorphin between the 18th and 23rd GW in response to painful stimuli. Adaptation of the fetus to stress includes accelerated maturation, notably the maturation of the lungs and 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.[14,69] Cortisol, on the one hand, initiates accelerated maturation of the brain and 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 and parahippocampal region, the brain structures that contribute greatly to learning and memory, contain a large concentration of cortisol and CRH receptors. Consequently, these regions are susceptible to accelerated brain maturation which can cause different structural changes in the developing brain. Apart from structural changes, behavioral changes were also noticed. Stress-induced changes in the hippocampus include a decreased number of neurons and corticosteroid receptors, decreased a level of serotonin and decreased synaptic density on distinct hippocampal regions. These changes are associated with memory impairment and learning disabilities later in life. Behavioral changes associated with accelerated brain development include hyperalertness and impaired fetal responsiveness to novel stimuli. Fetal ACTH may also be a cause of irritability and diminished attention. In addition, ACTH affects movement coordination and muscle tonus which can be disturbed 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 correlated to pregnancies complicated with IUGR, preeclampsia, infectious diseases, diabetes, and twin pregnancies. Many neuropsychiatric disorders (ADHD, sleep disturbances, unsociable and inconsiderate behavior, schizophrenia, depressive and neurotic symptoms, drug abuse, anxiety) are marked as potential neurodevelopmental consequences of prenatal stress exposure.[69] Increased maternal stress during pregnancy can influence an infant's temperament and cognitive functions[113-115] and it may leave adverse effects on the child's learning and memory at age six.[116] However, it should be emphasized that infant cognitive development can be moderated enormously by increased mother's care and developed emotional mother-infant attachment.[115]

Etiology of many chronic diseases, diabetes, hypertension, and coronary disease[117] as well as psychiatric diseases, ADHD, cognitive impairments in children and later in adult life, can be found in the prenatal period.[118] These conditions and diseases may be consequences of the fetal adaptations, which happen due to suboptimal intrauterine conditions and change homeostatic regulation mechanisms, metabolism or organ structure and function. This is called early life programming or developmental programming.[117,119]

High maternal cortisol in pregnancy is associated with programmed outcomes even in childhood like hypertension, behavioral disorders, and altered brain structure.[118] Programming and fetal stress might have different effects on female and male fetuses.[120,121] Prenatal exposure to stress can create a greater risk of depressive symptoms, schizophrenia, ADHD in boys than in girls.[118] On the other side, high levels of maternal cortisol in early pregnancy are associated with more effective problems in girls. This was linked with the larger right amygdala volume measured by MRI, as mentioned in the previous section.[111]

CONCLUSION

Prenatal period is annotated with an opportunity for prosperous development of the fetus (including fetal cognitive development) but also it is a fragile period of great vulnerability to environmental effects. The fetus is exposed to numerous stimuli (e.g., tactile, chemical, auditory, etc.) which differently shape the brain structure and guide the brain's functional development. Prenatal 3D/4D US imaging has improved prenatal assessment of fetal structural, functional, behavioral development and assists in puzzle solving of fetal cognitive development.[122] In addition to ultrasound technology, recent advancements in fMRI and fMEG have made it possible to examine functional neurodevelopment as well. All of these tools should be used in the best possible way to learn more about the fetal neurodevelopmental events and provide the most stimulative environment for the cognitive development of the fetus.

Primary cortical areas and subcortical formations are fully developed and highly active in a newborn; thus cognitive functions at the end of the gestation rely on them. At term, there is also low activity in the association cortical areas.

Early action planning development and fetal motor learning are recognized in the 2nd trimester. Progression in fetal activity and behavior complexity reflexes the maturational processes in the brain stem and later on, in the forebrain structures (the diencephalon and cerebrum). It starts with the emerging of the spontaneous movements and culminates with the presumed preference for the sound of the mother's voice.

Functional thalamocortical and corticocortical connections are required for the linkage between the periphery and the cerebral cortex. That is needed for the establishment of the fetal awareness of noxious as well as other sensory stimuli and higher order sensory perception begins in fetal life.

Fetal learning and fetal memory possibilities are impressive. Even though considered as rudimentary, fetal memory is lasting longer than it was previously thought. A remarkable property of synaptic plasticity is shown in the primary auditory cortex even before the brain has reached full-term maturation.

Studies conducted by 4D US indicate that emotion-like behaviors and roots of emotions appear during fetal life. It has been suggested that facial expressions and emotion-like behaviors may represent some kind of fetal emotion and awareness.

Roots of many disorders and chronic diseases of adult age have been linked to adverse events and effects on the fetus. Cognitive impairments and deficits in childhood and adulthood (impaired learning and memory, intellectual disabilities, attention deficits, etc.) may also originate in prenatal life.

Investigation of fetal cognitive functions is still in its beginning, but it is certain that future advances in the application of new imaging methods, such as different 3D/4D US modes and fMRI, will enable a better understanding of the cognitive abilities and functions of the fetus. These techniques can help in early detection of abnormal brain development, that is, to allow early diagnosis and prevention of the brain dysfunctions and damage, and to assure in due time intervention and habilitation of affected children. Finally, It is of great importance to emphasize again that infant cognitive development can be moderated enormously by increased mother's care and developed emotional mother-infant attachment.

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