Prenatal and Perinatal Medicine and Psychology Towards Integrated Neurosciences: General Remarks and Future Perspectives

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Abstract

Prenatal and perinatal psychology and medicine is an interdisciplinary scientific field of research and practice with the scientific focus on prenatal and perinatal conditions of human life. Prenatal period of human life represents a crucial phase in human life during which crucial developmental processes and regulations take place and these serve as adaptation strategies and physiological capabilities for the next postnatal life´s periods. Moreover, it is generally accepted that experiences during critical periods of prenatal, perinatal and early childhood stages of life organize brain systems, and influence the immediate and long-term psychology and behavior of the individual. A great body of evidence indicates that human brain development is organized from the very early time after fertilization and human fetus exhibits behavioral patterns as well as processing of affective, social, sensory and other stimuli. New integrated approaches in the research of early fetal brain and human mind bring data elucidating unique processes involved in the complex human mind development. This rapidly developing field of integrated neurosciences in prenatal and perinatal medicine is reflected in growing knowledge and new fundamental findings in behavioral embryology, psychoimmunoneuroendocrinolgy, neurogenetics and neuroepigenetics, research of bonding and other scientific areas. New approaches in both research and clinical medicine could reinforce the current knowledge and establish new methods of primary and secondary prevention strategies as well as to contribute to the development of modern personalized medicine.

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Introduction

Prenatal and perinatal psychology and medicine is an interdisciplinary scientific field of research and practice with the scientific focus on prenatal and perinatal conditions of human life. It includes an integrated knowledge in obstetrics and gynecology, midwifery, pediatrics, endocrinology, neuroendocrinology, psycho-neuroendocrinology, reproductive medicine, psychiatry and child psychiatry, embryology, genetics, developmental psychology, child psychology, psychoanalyses and other psychotherapy, anthropology, human ethology, philosophy, theology, history, cultural psychology and social sciences. Prenatal psychology is often joined with perinatal psychology and includes interdisciplinary study of the foundations of health in body and mind. It explores the psychological and physiological effects and implications of the earliest experiences of the individual before birth (prenatal), as well as during and immediately after birth (perinatal) on the health and learning abilities of the individual (Fedor-Freybergh, 2011; Šoltés & Radková, 2011). The prenatal period of human life represents a crucial phase in human life during which developmental processes and regulations take place and these serve as adaptation strategies and physiological capabilities for the next postnatal life's periods. Thus, there is a fluent development of all the levels of functioning, enhancing all the unique competences and organization changes from the prenatal period through the whole life span of the individual. Because of all these consequences, the concept of human life's continuum becomes of special importance. According to this concept, the human life has to be considered as an indivisible continuum, where each of the developmental stages is equally important (Fedor-Freybergh & Maas, 2011). In this continuum, the individual represents an indivisible entity of all functions on physiological, psychological and social levels. The physical, biochemical, endocrinological and psychological processes represent a whole that cannot be divided. The continuum of life begins in utero. It is not possible to separate any stages of human development from the rest of an individual life's continuum (Figure 1). The life continuum is one of the basic needs in human life in order to maintain homeostasis and equilibrium (Fedor-Freybergh & Maas, 2011).

Basic Principles

The prenatal phase of human life is the most important and determining period from both psychological and physiological points of view. It is the time of crucial and integrated development of all organs as well as the basic determination of the next complex personality. The prenatal child undergoes learning by different mechanisms and experiences different adaptation strategies, which are necessary to stay alive. All these unique processes serve as a preparation for postnatal life. Prenatal stress, maternal depression, maternal separation, hormonal deviations, immunology disorders, infections of various kinds and environmental influences have impact on the fetal brain and its differentiation in neurotransmitter level and/or neuroendocrine development, disturbances and predispositions. It is generally accepted that experiences during critical periods of prenatal, perinatal and early childhood stages of life organize brain systems, and influence the immediate and long-term psychology and behavior of individual (Fedor-Freybergh, 2008; Fedor-Freybergh, 1999; Čatár G., Ondriska F., Mikolášová G.. 2011; Šoltés & Radková, 2011). The prenatal stages of life represent a unique opportunity for the primary prevention of psychological, emotional and physical disorders in later life (Fedor-Freybergh & Maas, 2011).

The basic conceptual neuroscientific framework of the field could be properly delimitated by traditional knowledge and new findings in the fields of behavioral embryology, genetic and epigenetic aspects of neural development, psychoimmuno-neuroendocrinology and neurodevelopmental consequences of prenatal and postnatal bonding.

Behavioral Embryology

Behavioral embryology is based on the knowledge of spontaneous as well as coordinated behavior of the human fetus. There is evidence for coordinated behavior of the human fetus to be stimulated by specific stimuli, including social stimuli.

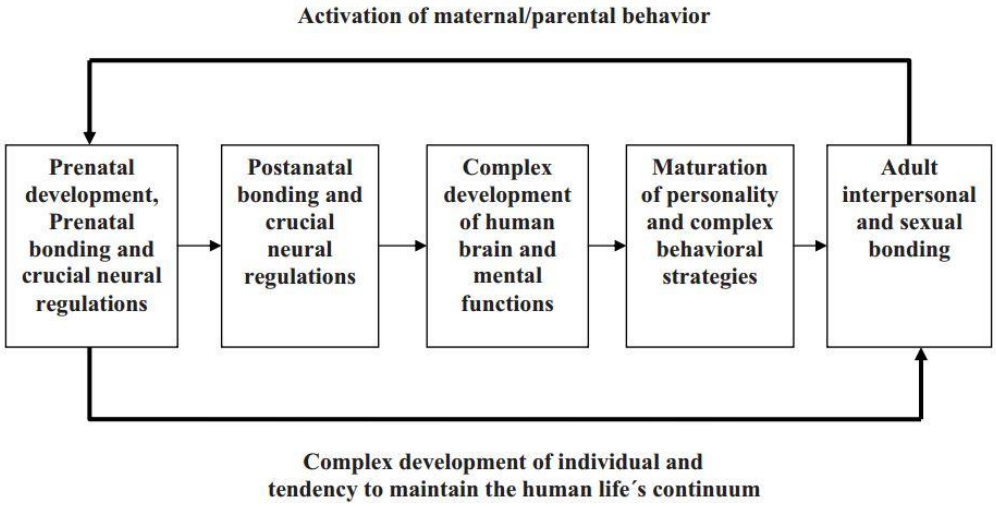

Figure 1: The concept of complex human development and human life´s continuum

Also it is very well known that there is an increase of spontaneous movement activity of the human fetus in time with final spontaneous decrease close to the time of birth. The very beginning of spontaneous movements of the human fetus is observed approximately 8 weeks after fertilization. At the age of 10 weeks after fertilization the human fetus is able to change its position in utero and disposes of wide range of behavior at the age of 15 weeks after fertilization (16 different kinds of movement), including independent movements of extremities, rotation, head movements, yawning, swallowing, breathing movements etc. It is suggested that a spontaneous decrease of fetus activity close to the end of gravidity is induced by the inhibitory action of the brain structures (Michel & Moore, 1999).

Assessment of motor development in the human fetus provides an opportunity to examine maturation of the central nervous system during gestation. During the third trimester, neuronal differentiation and synaptogenesis thrive in the cortical plate with afferent projections from the thalamus migrating deeper into the cortical layer increasing the probability that movement will be generated and modified in response to stimulation (Grant-Beuttler, M., Glynn, L.M., Salisbury, A.L., Davis, E.P., Holliday, C., Sandman, C.A., 2011). Normal fetal motility is used to be characterized by specific movement patterns for the body part which actively participates in the movement including initiation and continuation of the movement with head, arm, leg, trunk or combination of all, and non-specific movement patterns like total body activity, gross movements and trunk movements.

The fetal motility could be defined by the quantitative or qualitative analysis of the movement patterns recorded with ultrasound. Moreover, there are also fetal behavioral states which are defined as combination of specific movement pattern for eye movement, non-specific pattern for gross or body movement together with four classes of fetal heart rate patterns. Normal utterances of fetus motility in physiological pregnancy are characterized by a wide range of occurrence of each specific movement pattern and the ranking in the frequency of specific movement patterns is strongly age-related. The strongly age-related

gradual changes in temporal patterning of, for instance, general movements, breathing movements and clustering of movements (behavioral states), suggest influence of the central nervous system on which are superimposed the smaller influences of hormones (De Vries & Fong, 2006).

Fetal movement recorded with continuous ultrasound suggests that some general movements, such as fetal breathing and mouth movements increase, whereas other movements, such as startles, decrease with advancing gestational age. Grant-Beuttler et al., 2011) applied vibro-acoustic stimulation over the maternal abdomen to detect when during gestation a fetus is capable of producing a motor response. The authors suggest that following vibro-acoustic stimulation, an immediate increase of large, jerky movements suggests instability in fetal capabilities. Fetal movement quality changes over gestation may reflect sensorimotor synaptogenesis in the central nervous system. Fetal ultrasound studies suggest higher in degree of fetal maturation the smoother and more complex fetal movements are observed. The development of more complex movements as the fetus ages is an important indicator of motor development and may signal neurological development and motor learning. However, during periods of intense stimulation, such as the vibro-acoustic stimulation, fetal movements are characterized by higher frequencies of more immature and uncoordinated movement patterns. The changes in fetal movement at different ages and following vibro-acoustic stimulation appear to be part of the normal maturational process (Grant-Beuttler et al., 2011).

Moreover, human fetus also responds to sensory stimuli such as chemical (taste and smell), touch, pain and sound. And all of human sensory organs are already developed and functional before the birth. Because of all these well-developed capabilities it is suggested that early development of the ecological self (recognized as a one of the domains of human personality) already starts in utero (Fedor-Freybergh, 2008; Koukolík, 2008; Michel & Moore, 1999). Kachewar and Gandage (2012) in their study considered the fetal mind as a collection of brain functions and a reflection of functions of its organs of sense and of its inner self. They hypothesized that fetal brain reactivity could be objectively demonstrated by Color Doppler ultrasound evaluation of waveform patterns of the Middle Cerebral Artery of the fetal brain. The fetal Middle Cerebral Artery supplies almost 80% of the blood to the fetal brain and can give abundant information about fetal heart and fetal stress. They observed the normal waveform pattern with regular systolic and diastolic component in states of complete fetal health. But when the fetal inner self was traumatized by cardiac ectopics or arrhythmias, bizarre and aberrant patterns were observed to replace normal waveform. And when the entire fetus is under stress, as in cases of intra uterine growth retardation, changes are again manifested in the fetal Middle Cerebral Artery velocity waveform pattern and are designated as the fetal Brain Sparing Effect. The authors concluded that imaging evaluation of this vessel could reflect various effects of sense organs and brain contact as the function and information processing of the fetal brain. Thereby, it could be the unique non-invasive opportunity to observe the fetal inner self-expressions.

On the other hand, all these capabilities enable the human fetus to process a wide range of prenatal experiences, which induce learning and patterns potentially playing a role also in the postnatal period. Sensory stimulation could induce and organize important neuro-motoric development. For example, it is hypothesized that side differences in vestibular stimulation and perceptions could explain functional specializations of human brain hemispheres. The idea is that the human fetus prefers such in utero position in which the left side vestibular apparatus exhibits higher stimulation and its stimuli are therefore processed in the right brain hemisphere. This could be one of the explanations why fetuses as well as newborns exert higher degree of functional development of the right hemisphere. The human fetus faces very specific conditions in utero, which include movements of mother, movements of fetus itself (stimulation of vestibular apparatus), chemical properties of amniotic fluid, a lot of sounds from mother's body like intestinal sounds, heart rhythm, movements of diaphragm etc. There is also evidence for human fetus abilities to perceive and process mother's voice

and speech, including prosody and those are thought to be prominent to induce special human fetuses' reactions and learning, which could consequently serve as a pre-condition of high sensitivity to the mother's speech (melody and rhythm), the phenomena very well known in newborns, together with unique imitating and face emotional expression abilities. In this way, prenatal sound background could be significantly important experience for later postnatal cognitive, social and emotional capabilities (Michel & Moore, 1999; Fedor-Freybergh, 2008).

Genetic and Epigenetic Aspects of Neural Development

It is suggested that brain development could be influenced approximately by 2/3 of all human genes. Despite such complex genetic determination there is still a great body of knowledge that needs to be elucidated in all these unique actions and processes during human brain development. For now, only several genes are recognized to be clearly associated with the human brain development. For example, intense development of the human cortex is also co-regulated by the HAR-1 gene, which is very active in the Cajal-Retzius cells. These cells produce the reelin peptide which serves as a "guide" to create a typical architecture of the human cortex. Another gene FOXP 2 influences development of brain areas, which are involved in the human language development. Microcephalin and ASPM-1 genes also influence human brain development (Koukolík, 2008). Mutations or other inappropriate changes in these gene expressions could result in very serious consequences in brain development, maturation and mental and behavioral disturbances. For example, contactins are the neural cell-adhesion molecules and belong to the immunoglobulin superfamily of neural cell-adhesion molecules.

They represent major molecules for neuronal development and formation of synaptic contacts and also play a role in neuritogenesis, fasciculation of neurons, axonal and dendritic targeting, synapse formation and synaptic plasticity. Disruptions in contactin genes may increase the risk for autism spectrum disorders. The neural cell-adhesion molecules contactin 4, contactin 5 and contactin 6 may differ in binding properties as well as in effects on neurite outgrowth (Mercati, O., Danckaert, A., André-Leroux, G., Bellinzoni, M., Gouder, L., Watanabe, K., Y., Grailhe, R,. de Chaumont, F., Bourgeron, T., & Cloëz-Tayarani, I. 2013). Also the molecules known to be members of the SRY box-containing (Sox) family of transcription factors exhibit activity as important transcriptional regulators for the development and differentiation of multiple organ systems. Twenty Sox genes have been identified in mouse and human genomes. Several Sox genes are expressed in the developing central and peripheral nervous system and appear to regulate differentiation. For example, studies showed central role for Sox11 in regulating the processes of neurite growth and neuron survival. Special cell culture model showed that Sox11 knockdown increased expression of the proapoptotic gene BNIP3 (Bcl2 interacting protein 1 NIP3) and decreased expression of the anti-apoptotic gene TANK (TRAF family member- associated NF.B activator) (Jankowski, M.P., Cornuet, P.K., Mcllwrath, S., Koerber, H.R., Albers, K.M., 2006). Another family of transcription factors involved in brain development is the Pax factors determined by related Pax family genes with similar domain binding specifity (Carbe, Ch., Garg, A., Cai, Z., Li, H., Powers, A., Zhang, X., 2013). Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of secreted signaling molecules. Brain-derived neurotrophic factor is a potent regulator of neuronal development and synaptic plasticity that is fundamental to neural circuit formation and cognition. It is also involved in the control of energy homeostasis. Its dysfunctions with mutations in the genes for BDNF and its receptor, TrkB, could result in serious pathological conditions like Alzheimer´s disease, schizophrenia, depression and severe obesity in humans and mice (Vanevski & Xu, 2013). Another interesting finding comes from research of mitochondria DNA. It is well known that all the mitochondria DNA is only maternally inherited and that mean all DNA from the moment of fertilization during the whole life of the individual come exclusively from

the mother. And this finding is even more impressive since mitochondria are very well known to be extremely important for a lot of essential biochemical processes as well as for neuronal morphogenesis and differentiation (Hroudová & Fišar, 2011; Koukolík, 2008). On the other hand, pathophysiology of mitochondria is involved in the pathogenesis of many psychiatric disorders, behavioral disturbances, learning dysfunctions, circadian rhythms disturbances, eating and sleep disorders (Fišar& Hroudová, 2010; Hroudová & Fišar, 2011; Sharpley, M. S., Marciniak, C., Eckel-Mahan, K., McManus, M., Crimi, M., Waymire, M., Lin, C. S., Masubuchi, S., Friend, N., Koike, M., Chalkia, D., Macgregor, G., Sassone-Corsi, P., & Wallace, D. C., 2012; Lane, 2012) and ageing (Camus, M.F., Clancy, D.J., Dowling, D.K., 2012).

The very intense research during the last decades gives evidence for a special role of epigenetic mechanisms also to be markedly involved in the processes of development and organization of human brain functions. Epigenetic mechanisms play an important role in the regulation of gene expression in response to environmental signals and drugs and represent the interface of the genome and the environment without the gene´s mutation. There is an evidence for the interplay between sensory experience and innate genetic programs leading to the formation of neuronal circuits during early brain development. Recent evidence suggests that the dynamic regulation of gene expression through epigenetic mechanisms is at the interface between environmental stimuli and long-lasting molecular, cellular and complex behavioral phenotypes acquired during periods of developmental plasticity. Moreover, there is also evidence for important functions of epigenetic factors for embryonic neurogenesis (Fagiolini M., Jensen, C.L., Champagne, F.A.., 2009; Jakovljević, M., Reiner, Ž., Miličić, D., Crnčević, Ž., 2010; Jobe, E.M., Andrea. L., McQuate, A.L., Zhao, X., 2012). Several important mechanisms through which various stressors can operate, especially during rapid fetal development or early-life episode were recognized. Moreover, transgenerational epigenetic effects have been associated also with pathological conditions such as schizophrenia, depression, drug abuse, and social dysfunction in animals and humans (Murgatroyd, C., Wu, Y., Bockmühl, Y., & Spengler, D.., 2010; Pete & Akbarian, 2011; Welnhold, 2012). There are 3 main basic epigenetic molecular mechanisms, including DNA methylation, histone modification and microRNA dysregulation. (Fagiolini et al. 2009; Hsieh & Eisch 2010). All these epigenetic changes could be involved in pathophysiology of many disorders and pathological conditions, including psychiatric disorders. Very interesting data brought study of transgenerational transmission of trauma by Yehuda, R., Bell, A., Bierer, L. M., Schmeidler, J. (2008), (also reviewed in Yehuda 2011). The authors found offsprings of the Jewish parents who underwent an extreme psychic trauma during second world war (extremely stressful, life-threatening conditions including the Holocaust), recognized as posttraumatic stress disorder (PTSD), to have a lower plasma cortisol and higher risk to develop PTSD, especially in the case of maternal PTSD, and depression and anxiety in comparison to healthy controls (offsprings of parents without PTSD). Finally, multiple data analyses supported the suggestion that the main pathophysiological mechanism could be explained by epigenetic changes of glucocorticoid receptor´s gene.

The role of epigenetic modification has also been demonstrated in the postnatal mother-infant interactions in animal studies. Individual variations in maternal care during the immediate postpartum period in rats are associated with changes in offspring hypothalamic-pituitary-adrenal (HPA) activity, neuroendocrine systems involved in reproduction and hippocampal plasticity (Meaney, 2001).

Despite the rapidly growing body of research, the field of neuroepigenetics is still at its very beginning and only a few studies dealt with fetal or childhood exposures or outcomes. But early findings of behavioral epigenetics suggest such studies could provide insights into behavioral and mental health conditions.

Prenatal Psychoimmuno-Neuroendocrinology

It is very well known that there is a great deal of evidence for very close functional integration between nervous, immune and endocrine systems. It is characterized as immuno-endocrine-neurotransmitters-behavioral integration with multi-level interactions and influence of neuromediators, neuropeptides, cytokines, hormones and other molecules within unified interplay and integration, where each of the systems could influence the other in a physiological or pathophysiological way (Fedor-Freybergh, 1999; Song & Leonard, 2000). Stress (including psychological) promotes immune dysregulation, inflammation, impairs antibody responses to vaccination, slows wound healing, and suppresses cell-mediated immune function. Importantly, the immune system changes substantially to support healthy pregnancy, with attenuation of inflammatory responses and impairment of cell-mediated immunity. This adaptation is postulated to protect the fetus from rejection by the maternal immune system. Thus, stress-induced immune dysregulation during pregnancy has unique implications for both maternal and fetal health, particularly preterm birth (Christian, 2012). For example, there is evidence for higher risk for cerebral palsy and schizophrenia in the offspring of mothers who experienced infections during pregnancy. Moreover, prenatal stress and inflammatory processes during pregnancy have implications for fetal development. In non-human primates, repeated exposure to stress during pregnancy affected the transfer of antibodies across the placenta. Maternal stress can also indirectly alter offspring immune function through effects on preterm birth and fetal weight. In part because maternal antibodies are transferred to the fetus primarily in the final weeks of pregnancy, infants born prematurely are likely to have significantly impaired immune function. Furthermore, low birth weight has been associated with poorer antibody response to vaccination in adolescence, higher cortisol responses to acute psychosocial stress in adulthood, and increased risk of cardiovascular and metabolic disorders including diabetes later in life (Christian, 2012).

During critical developmental periods of the neuro-endocrine-immune system, neurotransmitters, hormones and cytokines, when occurring in unphysiological concentrations, and various toxic agents, can be effective as endogenous malorganizers and result in life-long functional disturbances and diseases (Fedor-Freybergh, 1999; Fedor-Freybergh & Maas, 2011). Many substances cross the placental barrier during pregnancy (stress hormones, ACTH, alfa-MSH, vasopressin, oxytocin etc.) and influence the neural and endocrine structures of human fetus (Fedor-Freybergh, 2008).

Stress and its influences on the human fetus during pregnancy are studied intensely and these studies bring interesting findings. Primary and a very important pathway of the effect of stress on the human fetus is the HPA stress axis (Sandman, C. A., Glynn, L., Wadhwa, P. D., Chicz-DeMet, A., Porto, M., & Garite, T. 2003; Sandman, C. A., Glynn, L., Schetter, C. D., Wadhwa, P., Garite, T., Chicz-DeMet, A., & Hobel, C. 2006). The human fetal nervous system undergoes enormous development, including migration, proliferation and differentiation of the brain cells.

By week 20 of gestation, axons form synapses with the cortical plate. This process continues so that by 24 weeks cortical circuits are organized. The enormous growth of the human fetal nervous system is characterized by the proliferation of neurons estimated to increase at a rate of 250,000 per minute. These unique processes are so intense that by 24 weeks after fertilization the cortical circuits are well organized (Cowan, 1979). Because of the dynamics and intensity of these changes, the human fetus is particularly vulnerable to both, organizing and disorganizing influences, the phenomenon known as “fetal programming”. Programming is a process by which a stimulus or insult during a critical developmental period has a long-lasting or permanent influence (Sandman & Glynn, 2009). Regarding stress to be an important factor influencing neural development, knowledge that the placenta expresses for gene CRH is taking a special importance. The key issue elucidating the stress-related effect is that on the one hand placental CRH increases maternal cortisol, while on the other hand it activates the promoter region of placental CRH gene (Sandman & Glynn, 2009). In such a condition the consequences of stressful events during pregnancy

become better understood: intense social or other kinds of stress in pregnant woman lead to increased maternal cortisol in plasma, which pathologically enhances the next production of cortisol by inducing the production of placental CRH and both mother and her fetus face increased levels of cortisol with potentially harmful effects.

The various and important effects of natural glucocorticoids on the central nervous system are known. Optimal levels of glucocorticoids are required for neuronal growth, differentiation, and survival, and they positively modulate synaptic plasticity and physiologically modulate early life programming of stress reactivity.

On the other hand, both animal and human studies showed that prenatal exposure to glucocorticoids excess, due to maternal endogenous overproduction or exogenous administration, may cause permanent behavioral changes in offspring and induce neuroendocrine and cardiometabolic lifelong disorders (Fietta, P., Fietta, P., Delsante, G. , 2009).

The study of Sandman and Glynn (2009) showed fetuses exposed to optimal placental CRH to exert an enhanced maturity, while fetuses exposed to higher levels exerted lower reactivity to stimulation. The authors suggest an important role of the placental CRH for fetal programming. Animal studies also demonstrated decreased DNA methylation of the corticotrophin-releasing-factor gene promoter and increased methylation of the glucocorticoid receptor exon 17 promoter regions in hypothalamic tissue of adult male mice born to gestationally stressed females. These epigenetic modifications are associated with exposure to stress during the early stages of prenatal development and may involve dysregulation of placental gene expression (Fagiolini et al., 2009). Animal studies also showed an important role for stress pathway dysregulation during prenatal or early life stress experiences, including prenatal stress, malnutrition, hypoxia, glucocorticoids exposure, smoking and drug abuse which increase sex – dependent risk for development neuropsychiatric disorders including major depressive disorder or schizophrenia.

It is suggested that the main role in these early life periods is played by intense interaction between gene expression and environmental influences and leads to increased developmental vulnerability. In some of these studies, analyses of expression and epigenetic patterns revealed changes in CRH and glucocorticoid receptor genes. Mechanistically, stress early in pregnancy produced a significant sex-dependent effect on placental gene expression supportive of altered fetal transport of key growth factors and nutrients (Goel & Bale, 2009; Chan & Zhang, 2011).

There is also increasing knowledge of the very important roles of the placenta in fetal brain development. For example, studies are consistently showing hormonal signals of maternal status, including glucocorticoids, insulin-like growth factors, insulin, and leptin, are sensed by the placenta and transmitted to the fetus predominantly through effects on placental function. In animal experiments, it was demonstrated that the placenta can convert maternal tryptophan into the neurotransmitter serotonin, providing the primary source of serotonin for the developing forebrain. Animal studies also suggest that the placenta has a mechanism for placental adaptations to adverse maternal environments that protect the developing hypothalamus at mid-gestation (embryonic days 11–13), an important period of neuronal proliferation and differentiation (Zeltser & Leibel, 2011).

Very important steroid hormones are progesterone and estradiol during human pregnancy. It is generally accepted that maternal LDL-cholesterol is a single substrate for placental synthesis of maternal progesterone. Despite this fact, it is not clear why the levels of progesterone are substantially higher in fetal as opposed to maternal blood. The fetal zone of fetal adrenal is suggested to have a role in the synthesis of progesterone precursors as sulfates of dehydroepiandrosterone (DHEAS) and pregnenolone (PregS). While the significance of C19 3.-hydroxy-5-ene steroid sulfates originating in the fetal zone of fetal adrenal for placental estrogen formation is mostly recognized, it is still not clear if maternal or fetal functions are more determining for excessive production of PregS in the fetal zone of fetal adrenal. Thus, it may be more convenient to utilize the fetal PregS than synthesis of

progesterone de novo. It is hypothesized that a possible explanation could be the function of 17.-hydroxysteroid dehydrogenase type 2, which is expressed in placental endothelial cells lining the fetal compartment and oxidizes estradiol to estrone and 20.-dihydroprogesterone to progesterone. This action could potentially serve to provide substances which may influence the placental production of progesterone and synthesis of neuroprotective steroids in the fetus, and also to create the hormonal milieu enabling control of the onset of labor (Hill, M., Pařízek, A., Jirásek, J.E., Jirkovská, M., Velíková, M., Dušková, M., Klímková, M., . .Stárka L., 2010). Moreover, progesterone and its isomers are suggested to have a pregnancy-stabilizing effect and estradiol to have a stimulating effect on the onset of parturition (Parízek, A., Hill, M., Kancheva, R., Havlíková, H., Kancheva, L., Cindr, J., Pasková, A., Pouzar, V., Cerny, I., Drbohlav, P., Hájek, Z., & Stárka, L 2005; Hill et al., 2007). As stated above, the gestation from the moment of fertilization is a critical "time window" during which a very intense interplay between hormones, neuromediators, cytokines, other substances and genes takes place. All these actions represent the unique interaction between maternal and fetal factors and various functions, but also determining interaction between genome and environment with possible long-lasting or ultimate consequences.

Prenatal and Postnatal Bonding

All mammalians already begin to live from the moment of fertilization as a part of the system which is represented by very close bonding between the fetus and the mother. Also, the newborn consistently preserves this special kind of bonding. While during the prenatal and early postnatal period the bonding is mostly physiological, during the postnatal period it is characterized by the qualitative shift from the bio-social to psycho-social level (Michel & Moore, 1999). There is a great body of evidence and knowledge that the degree of development in utero enables the human fetus to perceive and process a lot of sensory and even emotional and social stimuli, and that the fetus disposes of critical neurobehavioral regulations to be considered not "only the fetus", but the prenatal child (Fedor-Freybergh, 2008). The prenatal period is the most important, critical phase for brain development, which enables, if going well, to continue in the next very important postnatal development – the attachment period. It is characterized by unique interactions between mother and her child – postnatal bonding, which are necessary for complex human development.

This important life-time period is very intensely studied and described by Bowlby´s attachment theory. The theory reflects the importance of early, close mother-infant relationships and psychosocial factors for mental health and personality organization; functional interactions and essential neurobiological processes, including emotional, cognitive, social and other interactions (Shaver & Mikulincer, 2009; Hrubý, R., Hašto, J., Minárik, P., 2011). According to the theory, attachment is a strong offspring's tendency of proximity-seeking to significant others. Attachment behavior has developed during evolution to assure proximity and create special bonds to these significant others (caregivers). The child's proximity-seeking behavior is organized by the behavioral system and this complex behavioral strategy emerged in evolution to increase the likelihood of survival and reproduction (Hašto, 2006; Shaver & Mikulincer, 2009). The attachment emerges from special interactions between child and mother and is exclusively enabled by specific neural coordination of this essential quality during the critical early life period. These special bonding interactions have types of unique patterns, which are of significant importance to create essential neurobehavioral regulations for individual survival. There are several types of attachment, but generally it is useful to distinguish between secure and insecure attachment. The secure type is the physiological one and it is characterized by accessibility of the mother whom the child uses as a "safe base" as well as by the correct maternal evaluation of the child's signals to fulfill its needs (Hrubý et al., 2011). The complex developmental psycho-neurobiological model of attachment suggests secure attachment is a protective factor for psychosocial development, while insecure attachment occurs

significantly more often in patients with mental disorders (Agrawai & Gunderson, 2004; Hašto, 2006). Many studies have shown that insecure attachment is inversely related to well-being and positively associated with depression, anxiety, eating disorders, substance abuse, conduct disorder and personality disorders (Shaver & Mikulincer, 2009).

The progress of modern neuroscience enables interpretation of neurobiological aspects of attachment theory as multi-level neural interactions and functional development of important neural structures, effects of neuromediators, hormones and essential neurobiological processes including emotional, cognitive, social interactions and the special key role of mentalizing (Hrubý et al. 2011). Mentalizing or Theory of Mind could be explained as a man's ability to read other people's gestures and faces within identification of their underlying emotions and mental states (Frith & Frith 2005; Blakemore 2010). Mentalizing is closely related to the function of a neural mirror mechanism. In humans, the mirror mechanism is organized into two main cortical networks, the first being formed by the parietal lobe and premotor cortices, and the second by the insula and anterior cingulate cortex. Its role is to provide a direct understanding of the actions and emotions of others without higher order cognitive mediation (Rizzolatti, G., Fabbri-Destro, & M., Cattaneo, L., 2009). Such function and organization enable early identifications and emotional reactions and have an enormous importance for early mother-child interaction. It could be just the brain mirror system, which is fundamentally involved in the neural processes allowing us to share emotions, intentions and actions of others. The human brain has the unique ability to represent the mental states of the self and others and the relationship between these mental states, making possible the communication of ideas (Frith & Frith, 2006). Such neural processes underlying social interactions are already active in infants, exhibiting gradual enhancement during development.

A large body of research indicates that theory of mind typically develops in children during the first few years of life (Dumontheil I., Apperly I., Blakemore S.J., 2009). Mentalizing involves important emotional, cognitive and interpersonal processes and is suggested to be a pivotal factor in the evolution of attachment (Allen et al., 2008). The studies which used mentalizing tasks and neuroimaging methods showed activation of a network of regions including the superior temporal sulcus at the temporo-parietal junction, the temporal poles and the dorsal medial prefrontal cortex (Burnett & Blakemore, 2009; Blakemore, 2010). This network is considered to be the social brain and mentalizing is one of the wide ranges of actions within its unique capacity.

Having theory of mind in attachment relationships creates the human capacity for rapid development of the social brain and consequently cultural learning (Frith & Frith, 2005; Allen, J.G, Fonagy, P., Bateman, A.W., editors, 2008). Thus, the attachment relationship between infant and mother with its unique interactions and neurobehavioral regulations is critical for complex human development, including optimal social, emotional, and cognitive development (Strathearn, L., Fonagy, P., Amico, J., & Montague, P. R., 2009). As mentioned above, the period of prenatal and early postnatal bonding represents a very important life time phase during which crucial neurodevelopmental processes and basic coordination are enforced in order to develop and maintain the complex human capabilities necessary for complex human functioning (Figure 1).

Conclusions

Progress in science and medicine has brought an enormous knowledge about the unique importance of processes involved in the physiology and pathophysiology of human pregnancy, fetal development, perinatal and early life periods. There is great evidence for life span or long-lasting effects of complex multifactorial interplay during these periods, which are recognized from many points of view as a "critical window" to promote health or induce predisposition to pathological conditions. It is the time of crucial regulations and interactions on all levels of the developing individual organism. The rapidly developing field is reflected

by integrated approaches of prenatal and perinatal medicine and psychology. New approaches, increasing research and knowledge in many scientific disciplines even elucidate the unique processes of very early fetal brain and human mind development. New exciting findings indicate that the human fetus is from a very early life period more the prenatal child than "only the fetus" and is able to recognize and process a lot of stimuli including social and affective stimuli, and it also exhibits behavioral patterns and cognitive processing. Nowadays, we dispose of convincing scientific data to recognize development in utero as a crucial period for human brain development as indicated by research findings in behavioral embryology, neurogenetics and neuroepigenetics, prenatal psychoimmuno-neuroendocrinology, prenatal and postnatal bonding and other areas. Now it is clear that prenatal period represents a special developmental period which gives rise to necessary neural regulations for complex human development. This idea is reflected by the concept of human life´s continuum, in which the individual represents an indivisible entity of all functions on both, physiological or physical psychological and social level and which organizes itself from the moment of fertilization. Approaches of modern integrated neurosciences enable us to gain new insights in the understanding of complex human brain development and functioning. It gives us opportunity to assess the human mind as a dynamic organization of unique mental processes and continuous mutual interplay between various domains of human capabilities including affective, social and cognitive competences. All these unique features of human mind could be studied by various scientific fields and integrated approaches since the physical, biochemical, endocrinological and psychological processes represent a whole that cannot be divided.

The continuously developing field of prenatal and perinatal medicine brings also benefits in current clinical medicine and promising targets in future. Nowadays, laboratory screening methods are developed well and became a common part of diagnostics and clinical assessment before and during pregnancy. It is possible to detect changes in hormones levels, antibodies, inflammatory proteins or other substances in blood or amniotic fluid. Also genetic screening is established well by introduction of various prenatal techniques and further developed especially by methods of molecular biology. For example, the rapid detection of most common chromosomal (trisomy 21, trisomy 18, trisomy 13) and gonosomal aneuploidies in second–trimester amniotic fluid is possible using the QF–PCR method (Svecová, I., Burjanivová, T., Krsiaková, J., Lasabová, Z., Biringer, K., Kapustová, I., Móricová, P., & Danko, J. 2013). The next research and development of new methods in molecular biology will probably bring other breaking insights into pathology, diagnostics and treatment of serious disorders. New research data suggest that a very promising area for the next development of new diagnostic and treatment strategies could be molecular biology approaches, including research into the epigenetic aspects in many physiological or pathological conditions. For instance, animals studies show early embryonic exposure to maternal glucocorticoids can broadly impact physiology and behavior in offspring. The juveniles exposed to experimentally-increased maternal corticosterone during their embryonic phase had a protracted decline in corticosterone during the recovery phase of the stress response. In addition, embryonic exposure to corticosterone resulted in higher levels of reactive oxygen metabolites and an over-representation of short telomeres. In many species, individuals with higher levels of oxidative stress and shorter telomeres have the poorest survival prospects. Thus, long-term costs of glucocorticoid-induced phenotypes may include accelerated ageing and increased mortality (Haussmann, M.F., Longenecker, A.S., Marchetto, N.M., Juliano, S.A., Bowden, R.M., 2012).

In humans, the experience of stress during pregnancy is associated with increased risk of preterm birth, reduced birth weight, and smaller head circumference and has been implicated in the heightened risk of metabolic and psychiatric disorders. Maternal exposure to stress during pregnancy is associated with significant alterations in offspring neurodevelopment and elevated maternal glucocorticoids likely play a central role in mediating these effects. Placental 11b-hydroxysteroid dehydrogenase type 2 (HSD11B2)

buffers the impact of maternal glucocorticoid exposure by converting cortisol/corticosterone into inactive metabolites and targeted gene deletion and pharmacological studies suggest a functional consequence of 11b-hydroxysteroid dehydrogenase for the development of the hypothalamicpituitary response to stress. Animal molecular studies indicate regulation changes and epigenetic effects of prenatal stress in both, placenta and fetal brain. For example, prenatal stress was associated with a significant decrease in HSD11B2 mRNA, and increased DNA methylation at specific CpG sites within the HSD11B2 gene promoter in the placenta. Within the fetal hypothalamus, prenatal stress induced decreased CpG methylation within the HSD11B2 promoter and increased methylation at sites within exon 1. All these findings implicate DNA methylation as a mechanism by which prenatal stress alters HSD11B2 gene expression (Jensen Pena, C., Monk, C., Champagne, F.A., 2012).

On the other hand, results of recent studies imply that there is a degree of plasticity that remains in the adult for alterations in gene expression by epigenetic modification, which could promote the reversibility of induced phenotypic effects. Those findings suggest that aberrant phenotypes induced in utero or during early development can be potentially rescued. Research exploring methods of restoring aberrant phenotypes suggests promising development in diagnostics and treatment in susceptible patients. Those patients might be identified by means of screening for epigenetic markers during early life, which could be useful for treatment strategies in the future. In this way, epigenetics provides a probable target for pharmacological therapies (Chen & Zhang, 2011). New emerging findings and enormous scientific progress suggest that the next rapid development in the field of prenatal and perinatal medicine and psychology. The current knowledge reveals new perspectives in integrated approaches in both, research and clinical practice. New promising contributions to the field could be expected from continuous research and development in molecular biology, bioinformatics, systems dynamics, developmental neuroscience, social, cognitive and affective neuroscience and other disciplines supporting integrated approaches with special emphasis on those related to integrated neurosciences. Such new approaches could reinforce the current knowledge and establish new methods of primary and secondary prevention strategies as well as to contribute to the development of modern personalized medicine.

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