ANTENATAL TREATMENT WITH GLUCOCORTICOIDs AND THE HYPOTALAMIC-PITUITARY-ADRENAL AXIS

ANTENATALNA TERAPIJA GLUKOKORTIKOIDIMA I HIPOTALAMO-HIPOFIZNO-ADRENALNA OSOVINA

Milica Manojlović-Stojanoski1, Nataša Ristić1, Sandra Singh2, Verica Milošević2

1Institute for Biological Research »Siniša Stanković«, University of Belgrade, Belgrade, Serbia
2Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Serbia, Belgrade, Serbia

Summary

Fetal development is a critical period in the life cycle which is why the placenta provides a structural and physiological barrier that protects the fetus from the outer fluctuations and inner disturbances. A variety of influences from the environment, however, might induce fetal overexposure to glucocorticoids that target the fetal hypothalamic-pituitary-adrenal (HPA) axis and influence the fetal growth trajectory. Development of the HPA axis starts in the early stages of pregnancy, but the timing of HPA axis maturation and the glucocorticoid receptor (GR) expression in relation to birth is highly species-specific. The functional state of the fetal HPA axis plays a key role in the maturation of many organs necessary for intrauterine development and existence after birth. A functional HPA axis in near-term fetuses provides an adequate response to stress and also affects the timing of parturition. Due to their potent effect on the maturation of fetal tissues, synthetic glucocorticoids are used in human pregnancy at risk of preterm delivery. Dexamethasone and betamethasone, as the ones most commonly used, cross the placental enzymatic barrier (11\(\beta\)-hydroxysteroid dehydrogenase type 2 – 11\(\beta\)-HSD2) and have 25-fold higher affinity to the GR than endogenous glucocorticoids, stimulating many aspects of fetal maturation. Despite the numerous positive effects, exposure to synthetic glucocorticoids during fetal development may result in intrauterine growth retardation and fetal programming of the HPA axis function which is associated with cardiovascular, metabolic and psychiatric disorders manifested later in life. Long-term consequences indicate the need for the implementation of new studies that will provide new insights into the mechanisms of glucocorticoid action in fetal development.

Kratak sadržaj

Fetalni razvoj predstavlja kritičan period tokom životnog ciklusa, zbog čega placenta obezbeđuje strukturnu i fiziološku barjeru koju štiti fetus od spoljašnjih kolebanja i unutrašnjih poremećaja. Brojni uticaji iz okruženja mogu dovesti do izlaganja fetusa povišenoj koncentraciji glukokortikoida koji deluju na fetalnu hipotalamo-hipofizno-adrenalnu (HPA) osovinu i utiču na rast. Razvoj HPA osovine počinje veoma rano tokom gestacije, ali vreme njenog sazrevaњa i ekspresije glukokortikoidnog receptora (GR) u odnosu na rođenje je specifično za svaku vrstu. Fetalna HPA osovina ima ključnu ulogu u sazrevaњu brojnih organskih organa tokom intrauterinskog razvoja. Usled snažnog uticaja na sazrevaњe fetalnih tkiva, sintetski glukokortikoidi se potrebuju tokom rizičnih trudnošća kod kojih postoji opasnost od prevremenog porođaja. Deksametazon i betametazon, kao najčešće korišćeni lekovi u antenatalnoj terapiji, prolaze enzimskom placentalnom barjeru i imaju 25 puta veći afinitet vezivanja za GR u odnosu na endogene glukokortikoide, stimuliraju mnoge procese sazrevaњa fetusa. Uprkos brojnim pozitivnim efektima, izlaganje sintetskim glukokortikoidima tokom fetalnog razvoja može rezultirati retardacijom rasta fetusa i programiranjem fetalne HPA funkcije. Nastale promene su povezane sa kardiovaskularnim, metaboličkim i psihijatrijskim poremećajima, koji se mogu manifestovati tokom životnog ciklusa. Dugotrajinje posledice antenatalnog tretmana ukazuju na potrebu za novim studijama, koje bi obezbedile bolje razumevanje veze između izloženosti povišenim koncentracijama gluko-
vide a better understanding of the link between glucocorticoid overexposure during fetal development and adverse outcomes in adulthood.

**Keywords:** programming, fetal development, HPA axis, dexamethasone, betamethasone, antenatal therapy

**Pregnancy and the HPA axis**

In adults, psychological or physical stress activates the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic corticotrophin-releasing hormone (CRH) stimulates adrenocorticotropic hormone (ACTH) release from the anterior pituitary, which, in turn, causes the release of adrenal glucocorticoids. Adrenal glucocorticoids are dominantly involved in protein, carbohydrate and lipid metabolism, and strongly affect immune response with the primary goal of achieving homeostasis. An elevated glucocorticoid level provoked by chronic stress exposure exerts long-term changes in negative feedback control at the hypothalamic and pituitary level, while rapid glucocorticoid feedback suppression of basal and stress-induced HPA axis activity is controlled through a central site of action and involves activation of the glucocorticoid receptor (GR) (1).

During pregnancy, numerous adaptations of maternal anatomy and physiology provide optimal conditions and maximal security for the developing fetus, from the environmental fluctuations and inner disturbances (2). The placenta represents a fetomaternal exchange barrier to many of the maternal factors, although sufficient amounts of nutrients and oxygen are delivered to the developing fetus, whereas fetal metabolic excretion products are removed, enabling optimal fetal growth (3). Although the placenta shows broad species-specific differences, the common histological structure includes the maternal blood vessels endothelium (endometrium) and the fetal blood vessels endothelium (chorion). At the earliest stage of development, the principal precursor of the fetal part of the placenta is the trophoblast, evident as a thin cellular layer surrounding the blastocyst. During implantation, the trophoblast becomes the chorion, which is in direct contact with uterine endometrial connective tissue and differentiates into syncytiotrophoblast, a multinucleated cytoplasmic mass or syncytiotrophoblast (endome
c

thelium). The functional part of maternal placenta evolves from the uterine epithelium. The placental exchange area is villous in primates and sheep, and has the form of a labyrinth in mice, rats and guinea pigs (4).

Placental endocrine function creates a unique endocrine milieu providing the production of hypothalamic and pituitary hormones, as well as growth factors. The quantity of synthesized adrenal and gonadal hormones, using substrates of maternal and fetal origin, indicates intensive steroidogenic activity in the placenta. Placental CRH is secreted in large amounts into the maternal and fetal circulation influencing the maternal and fetal HPA axis function. In human CRH immunoreactivity was present in hypotalam
c

mic paraventricular nuclei (PVN) as early as at 12 weeks of gestation, but intensive hypothalamic stimulation of pituitary corticotropes started from week 16–30 of gestation (4, 5). Further trophic support of the adrenal gland growth and differentiation by the released ACTH becomes evident from around mid gestation towards the term, but there is no clear correlation between the level of plasma ACTH and glucocorticoid concentrations, suggesting immaturity of the negative feedback regulation during fetal development. In rats, significant hypothalamic support of ACTH synthesis and release and promotion of adrenal gland growth and functional differentiation started later, during the last third of gestation. The functioning of negative feedback control was verified by the decreased CRH expression before birth (4, 6).

Contrary to the hypothalamic CRH, placental CRH is positively stimulated by the increasing cortisol level that additionally up-regulates CRH gene expression establishing a feedback loop (4). Circulating CRH influences fetal pituitary ACTH production and directly stimulates dehydroepiandrosterone (DHEA), dehydroepiandrosteronesulphate (DHEAS) and cortisol output from the fetal adrenals. The secreted DHEAS serves as a substrate for placental estrogen production due to aromatase activity. The created estrogen/progesterone ratio forces interconversion of the biologically active cortisol to inactive cortisone, thereby decreasing negative feedback drive of the higher control centers, and consequently hypothalamic CRH and pituitary ACTH output are enhanced and further stimulate the growth of fetal adrenal glands (7). In humans and primates, this mechanism has enabled the size of near-term adrenal glands to surpass several times the relative size of adult ones, primarily due to the enormously developed fetal zone, while the quantity of synthesized steroids 5 times surpasses the stimulated steroid production in adults. On the other hand, a centrally positioned fetal zone, responsible for androgen production during pregnancy, disappears during the postnatal period. In newborns, dramatic shrinkage of adrenal glands takes place due to involution of the fetal zone caused by apoptotic cell death (4, 8). In rodents, as short gestational period species, adrenal glands synthesize glucocorticoids and aldosterone, but they are unable to produce androgens (9). Instead, androgens are produced during gestation in the placenta, maternal cor-

Ključne reči: programiranje, fetalni razvoj, HPA osovin, deksametazon, betametazon, antenatalna terapija
HPA axis functioning during in utero development

Prenatal presence of the GR has been demonstrated in the tissue derivatives of all three germ layers using in situ hybridization and immunocytochemical techniques. Strictly defined temporal and spatial expression of the GR, in fact, defines the target tissues and periods of glucocorticoid sensitivity during development. The established increase in GR mRNA amount just before the final differentiation step for each glucocorticoid target tissue, and the following decrease in GR mRNA amount upon differentiation, suggest that maturational events are controlled by glucocorticoids (11).

Activity of the fetal HPA axis and the released glucocorticoids direct the fetal growth trajectory to a considerable extent, according to the maternal energy resources. Glucocorticoids promote fetal maturation, as they affect the developmental and maturational processes of a variety of tissues and organs, in order to enable functional adaptations requested for extraterine survival. Under constantly changing environmental conditions, the survival of newborns depends on the maintenance of homeostasis, thermogenesis and a stable energy supply, in view of the transition from placental to enteral nutrition (12). To achieve this, glucocorticoids influence the timely differentiation of vital organ systems, including the central nervous system, gastrointestinal system, as well as other endocrine axes and tissue hormones sensitivity. Fetal lung maturation and surfactant production, enhancement of gluconeogenic enzyme activities in the liver and glycogen deposition, as well as adaptive thermogenesis in brown adipose tissue are also controlled by glucocorticoid action (12–14).

Like in adults, where stress implicates an HPA axis response, adverse intrauterine conditions in fetus also provoke fetal HPA axis activation (15). For example, fetal hypoxemia leads to an increase in the fetal ACTH concentration with up-regulation of mRNAs of the ACTH receptor and steroid-synthesizing enzymes in the adrenals that result in selective increase of cortisol synthesis in fetal sheep (16). Negative feedback control of the HPA axis by glucocorticoids begins to operate near the term, suggesting that active control of the glucocorticoid level is indispensable even during fetal development (17).

Coordinative activity of the HPA axis and the placenta in fetuses plays an important role in determining gestation length, which is certainly closely related to the maturation level of numerous organ systems. Although the exact mechanism remains unclear, an increase in fetal HPA activity has been established in humans and primates during late gestation. An increased cortisol concentration, that is generated locally in the placenta or derived systemically, stimulates prostaglandin synthesis, decreasing its metabolism, which results in an enhanced prostaglandin output. Huge amounts of DHEAS, produced by the fetal adrenals, undergo aromatization in the placenta and subsequently lead to elevated circulating estrogen levels (18). The created hormonal milieu and enhanced output of prostaglandins induce the expression of oxytocin receptors indispensable for uterine contractility. Late in gestation, an increase in unbound CRH fraction intensifies circulation in the feto-placental unit, potentiating the effects of local mediators and hormones that further up-regulate myometrial contractility and represent an important step in the initiation of birth (4, 19).

Antenatal treatment

Fetal growth and the development of fetal tissues and organs are dependent on many factors, including the hormonal environment. As mentioned, endogenous glucocorticoids produced by the fetal adrenal glands have a crucial role in these processes and exert beneficial effects on the maturation of fetal tissues where GR have been located. The timing of HPA axis maturation and expression of the genes encoding GR in relation to birth is highly species-specific. In species with a long gestational period (sheep, guinea pigs, primates and humans) that give birth to mature young, maximal brain growth and many aspects of neuroendocrine maturation take place in utero. But in species with short gestational periods (rats, rabbits and mice) that give birth to immature offspring, much of the neuroendocrine development, GR genes expression as well as the final maturation of endocrine axes occur in the postnatal period (20). Under normal circumstances, glucocorticoid levels are significantly lower in the fetus than in the mother and transplacental glucocorticoid diffusion is normally limited by the actions of the placental barrier enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (21). This enzyme plays a key role in regulating glucocorticoid concentrations in the fetal circulation by inactivating maternal glucocorticoids at the level of the placenta, and protects fetuses from glucocorticoid overexposure. In a rat and human study, it has been demonstrated that attenuated activity of 11β-HSD2 due to carbenoxolone application, maternal exposure to stress or antenatal treatment with synthetic glucocorticoids may expose the fetus to inappropriately high levels of glucocorticoids, which leads to reduced fetal growth followed by long-lasting consequences (12).

Due to their potency in maturating tissues and organs, synthetic glucocorticoids have been used for more than 40 years in human pregnancies at risk of preterm delivery. Antenatal glucocorticoid administra-
tion is perhaps one of the most effective prenatal interventions for the prevention of complications related to preterm birth, which include respiratory distress syndrome (RSD), intraventricular hemorrhage and, most importantly, neonatal mortality. The origin of this practice comes from Liggins and Howie (22), whose preliminary results indicated a reduction in the incidence of RSD and mortality in humans after maternal betamethasone treatment. Subsequent trials have confirmed the efficacy of this treatment in the reduction of complications associated with preterm delivery (23). According to the National Institutes of Health (NIH), all the fetuses between 24 and 34 weeks of gestation at risk of preterm delivery are potential candidates for antenatal glucocorticoid treatment. The recommended treatment consists of two doses of 12 mg betamethasone administered intramuscularly 24 h apart, or four doses of 6 mg dexamethasone every 12 h. They cross the placental barrier, have 25-fold higher affinity to the GR than endogenous glucocorticoids, and act in accordance with its nuclear transcription factor function (24). The question of the relative risk and benefit of repetitive courses of prenatal glucocorticoid administration is still open.

Antenatal glucocorticoid therapy is indicated in women with premature rupture of membranes and women with progestational or gestational diabetes at risk of preterm delivery, but contraindicated in cases of maternal systemic infections including tuberculosis (24).

During gestation, synthetic glucocorticoids are also used to treat several other clinical conditions of the mother, such as autoimmune diseases, allergies and asthma. The incidence of congenital adrenal hyperplasia (CAH) in fetuses is rare, but treatment with glucocorticoids is necessary to improve later outcome. In contrast to antenatal therapy applied in preparation for preterm birth, treatment under these clinical conditions often begins early in the pregnancy and lasts throughout gestation (25).

Figure 1 Synthetic glucocorticoids, such as dexamethasone and betamethasone, are used in antenatal therapy, cross the enzymatic placental barrier (11ß-hydroxysteroid dehydrogenase type 2 – 11ß-HSD2) and lead to fetal glucocorticoid over-exposure. They affect GR/MR expression in the hippocampus and cause inhibition of the HPA axis function during fetal development. Molecular and cellular changes established during fetal development reflect on postnatal functioning of the HPA axis. The altered set point of HPA axis feedback regulation from the hippocampus leads to HPA axis deregulation under basal and stress conditions in offspring. Alterations of HPA axis functioning in adults, due to fetal glucocorticoid over-exposure, are associated with an increased risk of cardiovascular, metabolic and psychiatric disorders.
Despite the mentioned positive effects, repeated doses of antenatal glucocorticoids have potentially negative effects on fetal growth and adverse effects on brain growth and development in animals and humans. Impaired intrauterine growth and low birth weight, as markers of an adverse in utero environment, are associated with hypertension, glucose intolerance, insulin resistance, type 2 diabetes, dyslipidemia, obesity, reproductive and brain disorders in adulthood (20, 26). The phenomenon is known as programming. The concept of early life programming explains the link between prenatal environmental events, altered fetal growth and development, and later pathophysiology (27). Maternal undernutrition, placental insufficiency and exposure to glucocorticoids that includes maternal stress or antenatal glucocorticoid therapy are the most common conditions that lead to intrauterine growth retardation (IUGR) associated with programmed outcomes in adulthood. Such conditions ultimately result in fetal glucocorticoid overexposure, since they mediate the programming effects of nutritional and other environmental challenges during pregnancy (28). The nature of the modifications that occur as a consequence of glucocorticoid overexposure is dependent on the dose and timing of the exposure (Figure 1).

Antenatal glucocorticoid therapy reduces mortality and morbidity in preterm babies and at the same time increases the risks of dysregulation of the metabolic function and endocrine axes, including stress response, growth and reproduction (12). More randomized human follow-up studies are needed to better understand the short-term benefits and long-term consequences of antenatal exposure to synthetic glucocorticoids on development and health.

**Antenatal treatment and fetal HPA axis function**

Results from animal and human studies demonstrate that fetal glucocorticoid overexposure results in fetal growth retardation that persists for a prolonged period after birth. The developing HPA axis is especially sensitive to glucocorticoid overexposure, as they strongly affect the establishment of HPA axis structure and function (29). Glucocorticoids control the proliferative activity of cells at all the HPA axis levels, and influence the gene expression of receptors, enzymes, ion channels, as well as cytoarchitectural proteins. All these changes at the cellular and molecular level result in altered set points of the delicate hormonal feedback mechanisms that become evident during the life cycle, under basal or stress circumstances (12, 29, 30).

The hippocampus has a central role in the negative-feedback regulation of HPA axis by glucocorticoids which interact with the abundantly expressed GR and mineralocorticoid receptors (MR). Application of synthetic glucocorticoids during pregnancy provokes a sex-specific influence according to hippocampal mRNA GR and MR levels in fetuses. Single maternal Dx exposure results in significant increases in MR and GR mRNA in the CA1–2 region of the hippocampus, and MR mRNA in the dentate gyrus in female fetuses, while changes are absent in male guinea pig fetuses (31). After multiple maternal treatment with Dx, marked increases in MR mRNA level in the hippocampus of female fetuses were recorded, while in males enhancement of GR mRNA was shown in limbic structures indicating changed hippocampal feedback sensitivity to glucocorticoids, natural or synthetic (32). Quantitative in situ hybridization demonstrated that the MR mRNA level is transiently decreased after a single Dx injection in the mouse fetus (33). Synthetic glucocorticoids applied during pregnancy lead to reduction in brain weight in fetuses. Literature data show similar effects of fetal glucocorticoid overexposure in different species, including mice, rhesus macaques and humans, such as reduced hippocampal volume with a reduced number of pyramidal neurons and pronounced degeneration of neuronal perikarya and dendrites, resulting in a decreased number of synaptic contacts (34, 35). Epigenetic changes caused by antenatal treatment with synthetic glucocorticoids that alter genome-wide transcription and modify GR DNA binding in the fetal hippocampus during late gestation have been recently shown in guinea pigs (36).

The hypothalamus, as the main site for glucocorticoid negative feedback, represents a regulatory place where the stress response starts and terminates. Neurons in the parvocellular division of the hypothalamic paraventricular nuclei (PVN) synthesize both CRH and AVP, or only CRH, and their axons project to the median eminence where the produced neurotransmitters are released. Repeated fetal glucocorticoid exposure to synthetic glucocorticoids, dexamethasone or betamethasone, inhibits fetal HPA function, as significantly decreased levels of CRH mRNA in the hypothalamic PVN in both male and female fetuses were established (32). Delay of CRH release in the external zone of the median eminence, shown by immunocytochemistry, might further confirm the decreased synthetic activity of CRH neurons in the fetus and neonatal offspring after fetal Dx exposure (37). Delicate cellular and molecular changes caused by the changed glucocorticoid milieu during development become evident at the level of hypothalamic neurosecretory cells morphometric parameters in fetuses and during the neonatal period (38). Analysis of neurosecretory parvocellular and magnocellular PVN neurons suggested that the area and diameter of neurosecretory cells nuclei at the levels were CRH neurons are dominantly positioned are significantly changed under the influence of dexamethasone, but the range of changes depends on the timetable and dosage of dexamethasone applied (39).
As a consequence of the antenatal treatment, the quantity and time profile of hypothalamic CRH released into the hypophyseal portal blood along with other ACTH secretagogues such as AVP change, and this reflects on the differentiation and activity of anterior pituitary corticotropes and the secreted ACTH. Prenatal glucocorticoid exposure also directly influences the fetal pituitary, as GR are present in pituitary primordial cells. Again, the timing and regime of fetal glucocorticoid exposure in utero will determine the outcome, as regards the establishment of hormone-producing cell populations in the anterior pituitary. Glucocorticoid impact on the proliferative activity of immature and differentiated ACTH cells results in a decrease of their number in near-term rat fetuses (40, 41). Multiple Dx administration during the last third of rat gestation also provokes marked inhibitory ultrastructural changes, most prominent at the level of synthetic organelles such as the endoplasmic reticulum and Golgi complex, accompanied by reduced ACTH levels during the fetal and neonatal period (39). On the contrary, in sheep fetuses, Dx exposure early in pregnancy resulted in a transient but significant decrease in plasma cortisol levels, followed by significant elevation in both female and male near-term fetuses. This may be attributed to an increased expression of the key steroidogenic enzymes in the adrenals, such as P450C 17 and 3-HSD mRNA in female fetuses. In the adrenal glands of male fetuses other types of changes have been reported including a reduced expression of ACTH receptor mRNA level (42).

Maternal glucocorticoid administration influences numerous processes during the establishment of fetal adrenal gland structure and function, including adrenal gland growth, formation of a centrally positioned medulla, expression pattern of the key steroidogenic enzymes, level of ACTH receptor expression, and consequently glucocorticoid output (43, 44). In rat fetuses, a marked decrease of the fetal adrenal gland volume as a consequence of the decreased proliferative activity in the adrenal gland periphery, which is the region of the adrenal cortex where most proliferating cells were found, has been established after intrauterine exposure to glucocorticoids (Figure 2). Even the mitotic activity of sympathoadrenal precursor cells – chromoblast that simultaneously migrate into the adrenal anlage and proliferate was inhibited under glucocorticoid influence (45, 46). Decreased expression of steroidogenic enzyme CYP17 after antenatal exposure to synthetic glucocorticoids has been reported, reflecting the persistence of the adrenal gland functional changes in guinea pigs (47). In fetal sheep, an acute effect of Dx exposure early in pregnancy resulted in a transient but significant decrease in plasma cortisol levels, followed by significant elevation in both female and male near-term fetuses. This may be attributed to an increased expression of the key steroidogenic enzymes in the adrenals, such as P450C 17 and 3-HSD mRNA in female fetuses. In the adrenal glands of male fetuses other types of changes have been reported including a reduced expression of ACTH receptor mRNA level (42).

**Figure 2** Central section of the adrenal gland of 21-day-old fetuses of control (C) and Dx treated (Dx) mothers during pregnancy. In control fetuses the main part of the adrenal gland is occupied by steroidogenic tissue composed of the zona glomerulosa (ZG) positioned at the periphery and inner zone (IZ), while in the central part formation of the adrenal medulla i.e. centripetal migration of chromoblast takes place. In the fetuses from Dx treated mothers the volumes of the adrenal gland and all its parts were significantly reduced.

**Antenatal treatment, HPA axis function and long-term consequences**

As presented, excessive glucocorticoid exposure during intrauterine development shapes the developmental profile at all the HPA levels, altering the set points of the offspring HPA axis feedback regulation. A decreased expression level of the GR and MR in limbic structures has been associated with reduced negative-feedback drive and increased HPA axis activ-
ity in offspring. Elevated basal corticosterone levels or a greater corticosterone response to stressful stimuli have been recorded, depending on the timing and dosage of fetal glucocorticoid exposure during pregnancy, in adult rats and sheep (48, 49). Sex-specific alterations in the HPA axis function and glucocorticoid output under basal or stress conditions during adulthood have been shown in guinea pigs as consequences of antenatal glucocorticoid exposure (50). In humans with low birth weight, increased cortisol response to stressful stimuli and ACTH hormone application as well as high fasting plasma cortisol levels were shown (51).

Growth retardation and the presented long-term deregulation of HPA axis function under glucocorticoid influence are the underlying mechanisms linking fetal development with postnatal health, including higher susceptibility to cardiovascular and metabolic diseases, as well as reproductive disorders (2, 52). Excessive glucocorticoid exposure causes major structural and metabolic alterations in numerous tissues during the period of tissue plasticity that actually represent an adaptive fetal response with permanent consequences (53). For example, glucocorticoids affect the development of the kidney by reducing the number of nephrons, influence the activity of the renin–angiotensin system and vascular responsiveness to angiotensin II, increasing the risk of cardiovascular diseases or hypertension in offspring subject to excessive glucocorticoid exposure during in utero development (54). Exposure to high glucocorticoid levels leads to a reduction of the insulin producing cells mass and their functional capacity during the fetal period. In addition, changed profiles of glucose tolerance and insulin sensitivity with enhanced glucose production and reduced glucose utilization in the major metabolic tissues, such as the liver, skeletal muscle and adipose tissue, become evident during the life cycle. Thus, the prenatal glucocorticoid environment might increase susceptibility to metabolic syndrome and metabolic diseases such as type 2 diabetes in adult offspring (55, 56).

Glucocorticoid exposure during early life creates an environment that the fetus recognizes as hostile conditions and this is followed by permanent changes in the HPA axis functioning. As a consequence, long-term neurodevelopmental changes might be provoked with adverse effects on neuromotor and cognitive functions, causing behavioral problems, even attention deficit hyperactivity disorders during adolescence (53–57). Even schizophrenia, anxiety or autistic disorders may be explained by the developmental origin of the disease hypothesis concept (58).

Emerging evidence from animal studies and several human studies suggests that prenatal epigenetic changes are, at least in part, linked to an increased risk for the development of mental diseases during the life cycle (59).

Concluding remarks

The HPA axis begins functioning during fetal development and controls several of its important aspects, including fetal tissue maturation due to enable adaptations requested for extrauterine survival, fetal stress response and the initiation of birth.

Antenatal glucocorticoid administration is often used in clinical practice when the risk of preterm delivery persists. Short-term beneficial effects of prenatal glucocorticoids in fetal tissue maturation are, at the same time, the ones that increase the long-term risks of different types of dysregulation manifested in adulthood.

Exposure to synthetic glucocorticoids during pregnancy provokes a sex-specific influence according to hippocampal mRNA GR and MR levels in fetuses that reflects on HPA axis function during in utero development.

Molecular and cellular changes established during fetal development reflect on postnatal functioning of the HPA axis. Sex-specific alterations in HPA axis functioning with reduced negative feedback drive from the hippocampus lead to increased HPA axis activity in offspring, under basal or stress conditions, depending on the timing and dosage of glucocorticoids applied.

A growing amount of information obtained from animal and human studies has offered evidence that link alterations of the HPA axis functioning due to fetal glucocorticoid exposure with an increased risk of cardiovascular, metabolic and psychiatric disorders.

Acknowledgements. This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Grant number 173009 and 175036 We would like to thank Company Krka FARMA d.o.o. Belgrade, Serbia for their kind donation of Dexamethasone Phosphate.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.
References


56. Dumortier O, Theys N, Ahn MT, Remacle C, Reusens B. Impairment of rat fetal beta-cell development by maternal exposure to dexamethasone by maternal exposure...


Received: January 15, 2014
Accepted: March 17, 2014