Maternofetal exposure to glicocorticoids and attention deficit hyperactivity disorder

Exposição materno-fetal a glicocorticoides e o transtorno de déficit de atenção e hiperatividade

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ABSTRACT
Pregnancy is a critical development period, in a way that small alterations can be crucial in shaping an individual's health for the rest of his life. Depending on wich adversive conditions the fetus is exposed to, like metabolic, hormonal and nutricional alterations by the mother, there is a higher susceptibility in developing certain diseases, syndromes and disturbs. Among the aforementioned adversities, we can mention the excessive use of synthetic glucocorticoids during pregnancy. It is known that glucocorticoids act at various levels within the fetal brain, physiologically modulating the individual's neurological function, and, by that, exposing him to cognitive decline and behavioral changes. This review aimed to explore some evidence of the impact of excessive glucocorticoid signaling on HPA axis modulation and consequent fetal adaptive changes, related to the vulnerability of the development of Attention Deficit Hyperactivity Disorder (ADHD). In view of the growing number of diagnoses of this disease, it is necessary to review medical recommendations, the use of these drugs by pregnant women and infants, and public health policies.

Keywords: gestation, HPA axis, fetal programming.

RESUMO
A gestação é um período crítico de desenvolvimento, de maneira que pequenas alterações podem ser determinantes em moldar a saúde de um indivíduo pelo resto de sua vida. Condições adversas às quais o feto é exposto, como alterações metabólicas, hormonais e nutricionais,

aumentam sua suscetibilidade ao desenvolvimento de doenças, síndromes e distúrbios. Dentre estas adversidades, destaca-se o uso excessivo de glicocorticoides sintéticos durante o período gestacional. Sabe-se que os glicocorticoides atuam em vários níveis dentro do cérebro fetal, modulando fisiologicamente a função neurológica do indivíduo e expondo-o a quadros de declínios cognitivos e alterações comportamentais. Assim, pode-se concluir que a exposição fetal excessiva aos glicocorticoides pode promover modificações importantes no funcionamento do eixo hipotálamo-pituitária-adrenal (HPA) que comprometem sua função e impedem o desenvolvimento corporal e cerebral usual do feto. Este comprometimento pode estar diretamente associado aos sinais clínicos do transtorno de déficit de atenção e hiperatividade (TDAH) observados. Frente ao crescente número de diagnósticos desta doença, faz-se necessário a revisão de recomendações médicas, do uso destes medicamentos por gestantes e lactentes e das políticas de saúde pública.

Palavras-chave: gestação, Eixo HPA, programação metabólica.

1 INTRODUCTION

The use of medications by pregnant women is common in medical practice, and in countries such as France, Canada, the United States, and Brazil, 80% of women use drugs during pregnancy. To these values, we can add the fact that the intrauterine period is marked by fetal metabolic programming that, in the face of possible maternal injuries, can permanently interfere in the structural, functional, and metabolic components of the fetus as part of an adaptive response to the environment in which it is inserted. Among these injuries are bad eating habits, lack of exercise, sleep deficit and, above all, the excessive use of medications such as synthetic glucocorticoids (OWEN, 2005; COSTA et al. 2017; MONTENEGRO YAH, 2019).

Glucocorticoid metabolism differs between the adult and the fetus, since maternal glucocorticoids can cross the placental barrier. The fetal hypothalamic-pituitary-adrenal (HPA) axis is partly responsible for regulating endogenous glucocorticoid production. Therefore, as this axis has not yet reached its full maturity, several enzymes play a key role in its regulation. Glucocorticoid signaling is marked by three distinct windows during the embryonic and fetal period, highlighting that both excessive signaling, mediated by prolonged synthetic administration, and lack of signaling can negatively impact fetal development and predispose individuals to develop diseases late in adulthood (OWEN, 2005; BUSADA, 2017; KATZUNG, 2017).

Thus, during gestation, fetal exposure to synthetic glucocorticoids has significant effects on the reduction of HPA axis activity. This condition is justified by the fact that some classes of glucocorticoids are not metabolized by the enzyme 11b-hydroxysteroid dehydrogenase (11b-HSD), expressed by the placenta and responsible for converting active cortisol into inactive

cortisol, thus being associated with a greater transfer of maternal cortisol to the fetus (OWEN, 2005; BUSADA, 2017; KATZUNG, 2017; MONTENEGRO YAH, 2019).

Moreover, the high level of plasma ACTH and, consequently, its prolonged action in the individual are associated with a reduction in the density of glucocorticoid receptors in the nervous system and an increase in the expression of the dopamine receptor, leading to failures in the formation of structural components of the prefrontal cortex, interfering in the behavioral and cognitive spheres, as happens in attention deficit hyperactivity disorder (TDAH) (KATZUNG, 2017; BENZING; SCHMIDT, 2019; CHEN et al., 2019).

ADHD, in turn, is characterized by a fragmented pattern of deficits in relatively independent cognitive domains. Characteristics of these cognitive domains generally include inhibition, decreased working memory, response variability, arousal, temporal information processing, activation, memory, decision making, delay aversion, impulsivity, hyperactivity, and inattention (BENZING; SCHMIDT, 2019).

In this sense, the study seeks to elucidate the direct relationship between exogenous glucocorticoid use during all phases of the gestational period and the development of ADHD in the offspring.

2 METHODOLOGY

A systematic review was conducted on the main changes caused by the use of exogenous glucocorticoids and their relation to the development of ADHD. The search was conducted for clinical studies, systematic reviews, and meta-analyses published in English and Portuguese in the PubMed, LILACS, Scielo, and CAPES Portal Periodicals databases from January 2012 to June 2022. In addition, we used papers found in a general search in the same databases with the same keywords but addressing their use in the titles and abstracts.

The key words used were "*glucocorticoid, neuronal development, pregnancy pharmacology, HSD3B2 enzyme, hypothalamus pituitary adrenal axis, dexamethasone, prednisone, cortisol, pregnancy, hippocampus, frontal lobe, ADHD, metabolic programming, fetal metabolism, maternal metabolism, types of glucocorticoids*". The following were used as filters: *clinical trials, systematic review* and *meta-analysis* in humans, full text and publication within the last 10 years.

3 RESULTS

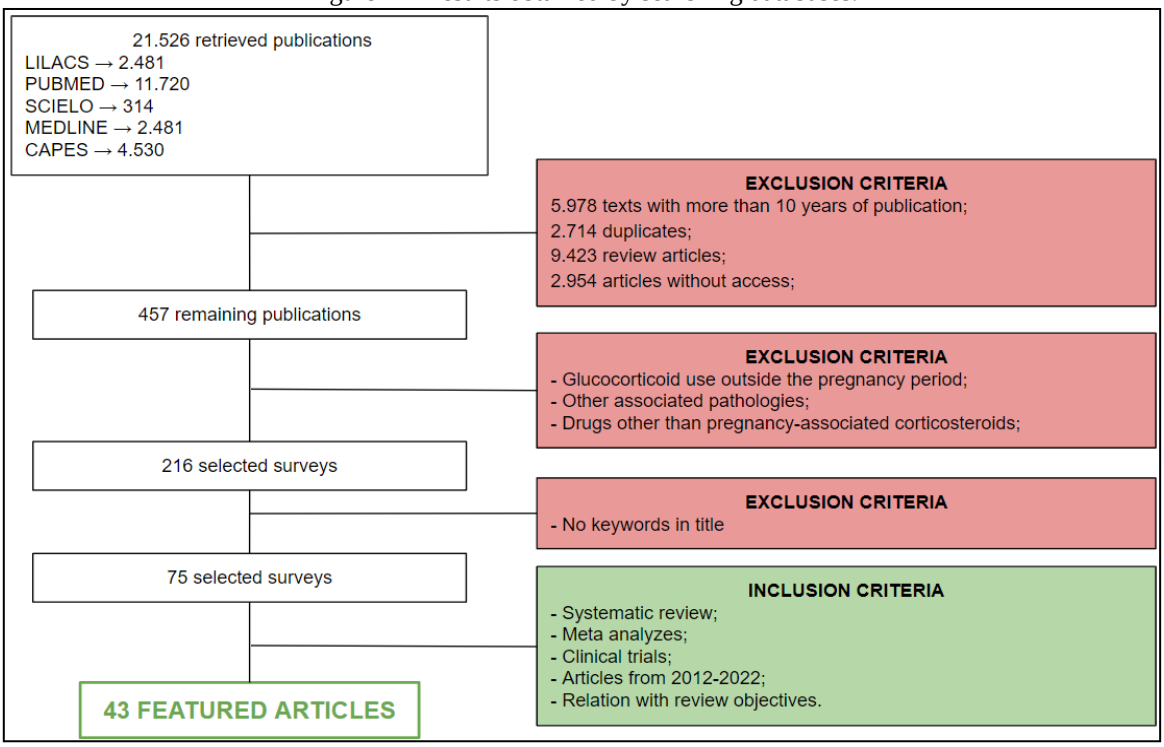
The selected articles underwent a critical evaluation to verify whether they adequately responded to the proposed objectives and guiding question. The search for existing

bibliographies was based on the methodology described, and after its application, we obtained 56 articles included in this systematic review.

The productions found in the databases totaled 21,526 articles, being 314 in Scielo; 2,481 in MEDLINE; 11,720 in PUBMED; 2,481 in LILACS, and 4,530 in the CAPES portal. The articles were numbered according to chronological order and the data were analyzed according to thematic approaches.

Considering the exclusion and inclusion criteria applied (Figure 1), we subjected the search to these, excluding texts older than 10 years of publication; other associated pathologies; drugs other than corticoids associated with pregnancy; repeated articles; treatment of ADHD; review articles; other target population; incomplete texts and paid texts, leaving 457 articles. The inclusion of the remaining articles occurred by searching for the key words, described in the methodology, in the titles of the articles, including those that had them and fit into articles of systematic review, clinical trial and meta-analysis, where we obtained 43 usual publications.

Figure 1 – Results obtained by searching databases.

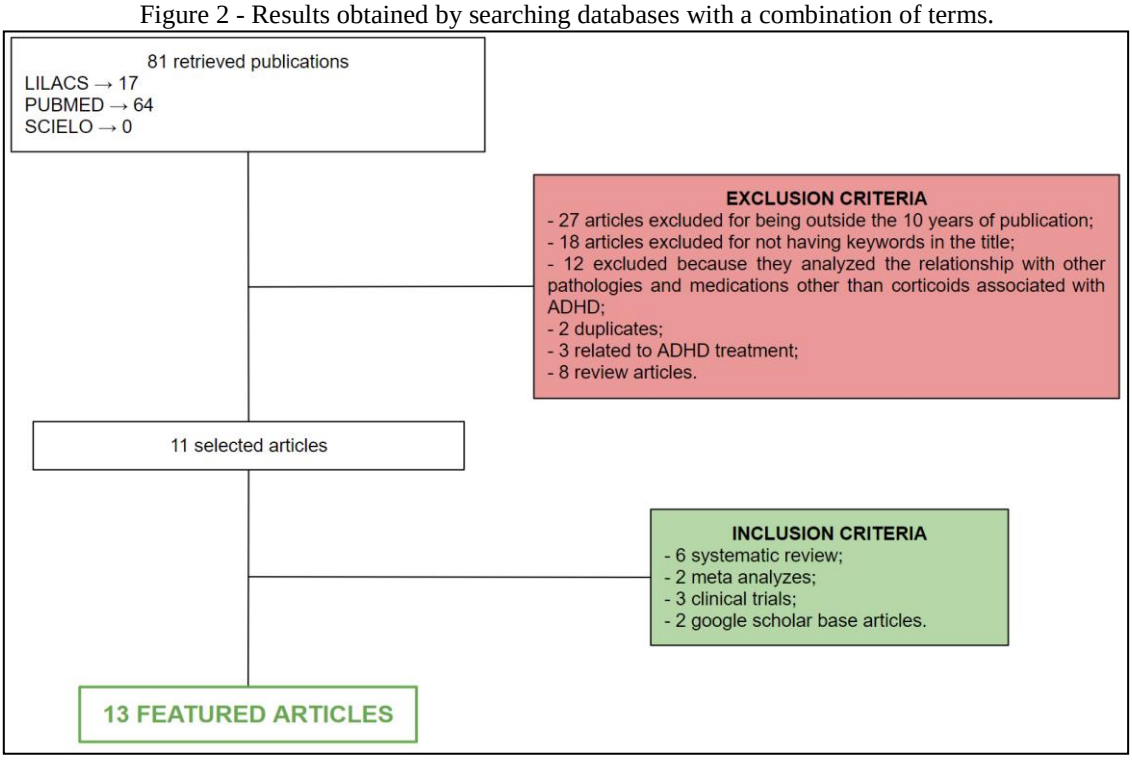


Authorship: Authors, 2023.

Furthermore, for the composition of the references, we also used the advanced search mechanism, which combines terms and words present in the text. Thus, after the combination of the words "ADHA" and "Glucocorticoid", we obtained 81 results in the Pubmed, Scielo and Medline platforms, 64 of which in Pubmed, zero in Scielo and 17 articles in Medline.

However, from these 81 results, we excluded texts older than 10 years of publication (29); texts without the terms in the title (18); other pathologies and other medications associated with ADHD (12), repeated articles (5), and treatment of the disorder (6). Thus, only 11 articles were selected for the composition of this bibliographic review. Moreover, it was necessary for the authors to include 2 articles published in the "google academic" platform to compose the chapter: "ADHD and its relationship", totaling 13 articles.

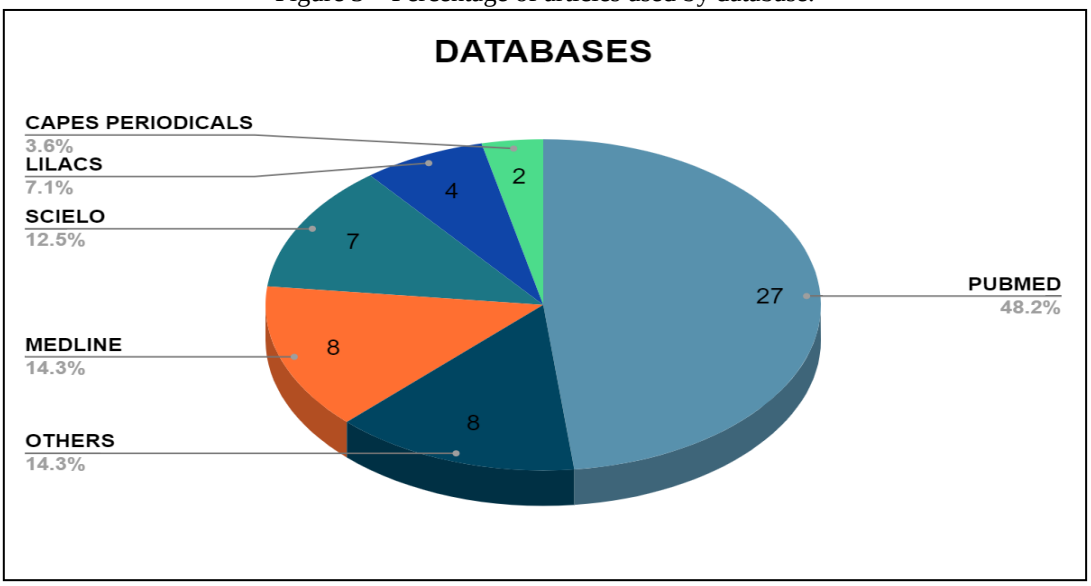
Figure 2 - Results obtained by searching databases with a combination of terms.



Authorship: Authors, 2023.

To these 13 results, the 43 obtained in the first search were added, thus totaling 56 articles read and compiled. Figure 3 shows the percentage relation of the composition of the databases of the references used. Of these, 27 were from the PUBMED database, corresponding to 48.2% of the references; 8 from MEDLINE, 14.3%; 7 from SCIELO, 12.5%; 4 from LILACS, 7.1%; 2 from the CAPES journal, 3.6%, and other databases, totaling 14.3%, that needed to be added for a better elaboration of this article.

Figure 3 – Percentage of articles used by database.



Authorship: Authors, 2023.

With the selected articles, it was possible to perform the quantitative references, classified into 4 variants (year, number of authors, modality, and type of publication). As for the year variant, a pattern of exponential increase in research related to ADHD and corticosteroids was found in 2017, and 3 articles from the year 2012 were selected, corresponding to 5.3% of all references cited. In 2013, 4 articles were selected (7.1% of all production). From the year 2015, 3 articles were selected (5.3%); in 2016, 9 papers (16%); 2017 was the year that had more results, 12 (21.5%) of all review; it was also obtained 7 articles from the year 2018 (12.5%), 6 articles from 2019 (10.7%), 5 articles from 2020 and 2021, corresponding to 9% each; besides 2 articles in 2022, 3.6% of the total articles included.

When analyzing the number of authors who produced each selected text, 9 of these, present 1 author, corresponding to 16% of the total; 12 (21.5%) 2 authors; 14 (25.0%) 3 authors and 21 publications, or 37.5% of the selected articles, were written by 4 or more authors.

The articles were divided into four subtypes: clinical trial, systematic review, meta-analysis and dissertation, representing 21.5%, 41%, 26.8% and 10.7%, respectively, of the texts included.

Finally, regarding the type of publication in terms of its place of publication, we found that about 46% of the references were published in journals; 20% in books; 20% in newspapers and 14% in other sites, including university sites and local publications.

Figure 4 - Characterization of the articles included in the review.

FEATURED ARTICLES	QUANTITATIVE ANALYSIS	
n = 56	NUMBER	%
YEAR		
2012	3	5,3
2013	4	7,1
2014	0	0,0
2015	3	5,3
2016	9	16,0
2017	12	21,5
2018	7	12,5
2019	6	10,7
2020	5	9,0
2021	5	9,0
2022	2	3,6
NUMBER OF AUTHORS		
1	9	16,0
2	12	21,5
3	14	25,0
4 or more	21	37,5
SUBTYPE		
Clinical trials;	12	21,5
Systematic review;	23	41,0
Meta analyses;	15	26,8
Dissertation;	6	10,7
PUBLICATIONS		
Journal;	26	46,0
Books;	11	20,0
Newspaper;	11	20,0
Others;	8	14,0

Authorship: Authors, 2023.

4 DISCUSSION

4.1 METABOLIC PROGRAMMING

Several studies indicate that the extrauterine environment has a strong influence on fetal development. Pregnant women who were the target of the stress caused by the attack on September 11th, 2001, in USA, had children with reduced cortisol concentration and babies susceptible to changes in their development (FALL et al, 2019). This condition can be explained by the concept of metabolic programming, introduced by David Barker in the mid-1980s. This is characterized by the adversities present in the intrauterine environment to which the fetus is exposed, promoting changes in its structural and/or systemic development, to adapt to the environment. In the long term, they may cause functional impairment to the individual and, consequently, a greater predisposition to several types of diseases (FALL et al, 2019; ROLDÃO, 2019; NORONHA; KALE; TORRES; COSTA; CAVALCANTI; SZKLO, 2017).

These changes occur in periods considered critical to development, in which the tissues have high cellular plasticity and are in an intense process of proliferation and differentiation. Faced with these moments, when adverse environmental conditions are observed, the developmental pathway can be redefined in an attempt to adapt to the changes the fetus is exposed to and prepare it for the type of environment it is likely to develop in (ALTARESCU, 2020; BARBOSA, 2020). The fetal period and the first year after birth are considered critical moments for the brain development of the individual. Injury from the environment in which the individual is inserted can directly influence its formation process, since the fetal brain is undergoing an intense process of synaptic formation (MONTENEGRO YAH, 2019).

After the end of neurulation, most of the billions of neurons that exist in the central nervous system are already formed and show intense cellular activity. However, it is in the fetal period, that neurons improve their specializations, through migration, connection and differentiation (GLOVER et al, 2017; PEARSON; TARABULSY; BUSSIÈRES, 2015). Between the 20th week of gestation and the early fetal period, the brain is already provided with the necessary structures for its mature functioning, but its cortical plate is still smooth. However, it is in the late fetal period that the specialization of the different regions of the brain occurs, and axons and synapses start to form in the cortical plate, progressing until early childhood. Thus, the fetal brain is vulnerable to injuries (MONTENEGRO YAH, 2019).

Several maternal adversities can impact fetal development, such as stress, anxiety, depression, post-traumatic stress disorders, microbiota composition, eating disorders, sleep impairment, and indiscriminate use of synthetic glucocorticoids. These factors are associated with increased serum glucocorticoids, due to their relationship with the hypothalamic-pituitary-adrenal (HPA) axis. This makes the axis highly susceptible to being programmed during development (PATRICK, STEPHEN, 2018). The consequent pathophysiological processes involved with the function of the HPA axis following prolonged maternal exposure to glucocorticoids are presumed to occur by epigenetic reprogramming in several biochemical pathways (MARCINIAK et al., 2017; BARBOSA, 2020; CASTRO, 2020). In humans, mutations in the 11βHSD-2 gene and increased fetal cortisol levels have been associated with intrauterine growth restriction (PERRONE et al, 2016). However, stress in the intrauterine environment is not only related to adult metabolic disorders, but also impacts the neuroendocrine and neurobehavioral system. Studies have shown an association between CRH (corticotrophin-releasing hormone) levels during pregnancy and cortical thinning, mainly in the temporal and frontal regions, directly related to the gestation time when stress is experienced and the stage of fetal brain development (PERRONE et al, 2016; MARCINIAK et al, 2017;

HANC, CORTESE 2018; ROLDÃO, 2019). Thus, studies evaluating mothers exposed to certain hormones, drugs and toxins, are conducted seeking to explore the period of maternal and fetal changes in gestation and how these influence the metabolic programming and future physical, mental and behavioral health of the offspring.

4.2 GLUCOCORTICOIDS AND THEIR RECOMMENDATIONS

To relieve the rheumatic pains of the gestational period, exogenous cortisol was first administered to pregnant women in 1948, two years after the advent of its synthesis in 1946. During subsequent years, its indications spread to the various medical specialties, including dermatology, endocrinology, oncology, ophthalmology, gynecology, and obstetrics (CASULARI; MOTTA, 2022; SACCONE; BERGHELLA, 2016; CUTOLO; IACCARINO; DORIA; GOVONI; SULLI; MARCASSA, 2013; LONGUI, 2007). However, side effects were observed in prolonged treatments, in which sodium retention with edema formation predominated. The unfavorable effects of these drugs were recognized, thus imposing limits on the use of glucocorticoids (GCs). In this sense, this aspect becomes a challenge to health professionals during the prescription of a drug, being necessary the risk-benefit evaluation for mother and fetus (TAVARES et al, 2021; RIBEIRO et al, 2017).

When they reach the maternal systemic circulation, glucocorticoids can behave in two ways. The first is their inactivation by the placenta, as occurs with prednisone and prednisolone, where less than 10% of the active drug is detected in the fetal circulation. While dexamethasone and betamethasone are not inactivated (NAKAI T, KITADA A, FUKUI S, OKADA M., 2021; BRUNTON, 2018). Corticosteroid therapy in pregnancy is appropriate for controlling maternal diseases that are clinically active by exogenous replacement in physiological doses, in the face of adrenal gland insufficiency (SACCONE; BERGHELLA, 2016).

During pregnancy, the administration of glucocorticoids is indicated for the treatment of children with structural heart disease associated with neonatal lupus and also for the cellular maturation of type II pneumocytes, consisting of increased production and secretion of surfactant and increased fluid absorption present in the lung, thus favoring its maturation for the postpartum period (PAULINO, 2021; M.D., 2016). To mature the fetal lung, administration is indicated in pregnant women between 24 and 33 weeks 6 days, whenever there is a risk of preterm delivery, including multiple gestations and premature rupture of membranes (PMBO). For pregnant women with gestational age 23 weeks and above, who are at risk of preterm birth within 7 days, based on a family decision, administration is indicated regardless of the presence

of RPMO and the number of fetuses, with betamethasone and dexamethasone being the drugs of choice (SAÚDE, 2012; PAULINO, 2021).

4.3 MATERNAL GLUCOCORTICOID METABOLISM

During pregnancy, women experience several changes in their organism mediated by the placenta. This organ secretes hormones and peptides responsible for neuroendocrine control in the maternal brain, in order to promote physiological changes that optimize fetal development and protect it from adverse events, thus achieving reproductive success. Serotonin and melatonin play important roles in determining maternal mood and behavior, both during pregnancy and in the postpartum period. Furthermore, TRH (thyrotropin-releasing hormone) is responsible for the release of thyrotropin hormone from the anterior pituitary gland. In high amounts, it is essential for stimulating the secretion of the prolactin-like hormone by the placenta. During the first trimester of gestation, increased expression of genes encoding different ligands and receptors that support the interaction between placenta and maternal brain have been observed (BEHURA SK et. al, 2019; BRUTON, 2018; PEARSON; TARABULSY; BUSSIÈRES, 2015).

Thus, the maternal hypothalamus plays a central role in regulating different fetal endocrine systems, such as the hypothalamic-pituitary-adrenal (HPA) axis. The regulation of the HPA axis will be critical to control fetal serum glucocorticoid levels (CAI, 2021; GJERSTAD, 2018; HERMAN, 2016). Moreover, high levels of progesterone also contribute to the increase in this physiological state by acting as antagonists of glucocorticoid (GR) and mineralocorticoid (MR) receptors, resulting in increased bioavailability of cortisol to the tissues (GJERSTAD et al, 2018; HERMAN et al, 2016).

The placental transfer of glucocorticoids to the fetus will depend on maternal metabolism, gestational age, binding, and storage proteins, the liposolubility of the drug, and its molecular size. The lower the binding to maternal plasma proteins, the easier the transfer of the drug from mother to fetus will be (PAULINO, 2021; LAUGESEN; BYRJALSEN; FROSLEV; OLSEN; SORENSEN, 2017). The mechanism of corticoid transfer from maternal metabolism to fetal blood circulation is influenced in gestation by the enzymes 11β-hydroxysteroid dehydrogenases, present along the trophoblast layer in the placenta, which catalyze reduction (11β-HSD1). The mechanism of corticoid transfer from maternal metabolism to fetal blood circulation is influenced in gestation by the enzymes 11β-hydroxysteroid dehydrogenases, present along the trophoblast layer in the placenta, which

catalyze reduction (11β-HSD2) (BRUNTON, 2018; LAUGESEN; BYRJALSEN; FROSLEV; OLSEN; SORENSEN, 2017; PEARSON; TARABULSY; BUSSIÈRES, 2015).

However, it is known that even though there is a metabolization that makes cortisol inactive, part of it reaches the fetal circulation. Dexamethasone and betamethasone - the glucocorticoids most commonly used by pregnant women - cross the transplacental barrier by 67% and 33%, respectively. This percentage is relatively high when compared with other glucocorticoids that are not recommended in the first trimester of pregnancy, such as prednisolone and hydrocortisone, which exceed the transplacental barrier by 10% and 15%, respectively (LAUGESEN; BYRJALSEN; FROSLEV; OLSEN; SORENSEN, 2017).

In addition, it is observed that after the ingestion of corticoids by the mother, it will interact with specific DNA sequences, called glucocorticoid response element sequence (GRE). Thus, GR-GRE drug interactions induce gene transcription, activating or inhibiting genes, such as COX-2, inducible NOS (NOS2), and inflammatory cytokines. Pregnant women with liver failure, promote increased bioavailability of glucocorticoids to the fetus, and may lead to the maturation of the fetal HPA axis, at the inappropriate time or ineffectively (BEHURA SK et. al, 2019; BRUNTON, 2018).

4.4 FETAL METABOLISM

The glucocorticoid guides a broad aspect of fetal development and is critical to enabling survival both in utero and after birth. Tissues responsible for immediate neonatal survival, such as the lungs, liver, brain, heart, and kidneys, are targeted primarily (FOWDEN, 2016; O'DONNELL et al, 2017; MORGADO et al, 2017). Direct cortisol secretion from fetal adrenal glands and consequent preparatory maturation for birth is possible through effective development of the HPA axis. While there is improved survivability, overexposure to glucocorticoids at a gestational age of increased vulnerability results in lifelong functional consequences. Thus, the increase in exogenous corticosteroids promotes deregulation of the negative feedback of the fetal axis, since it sensitizes its receptors, resulting in decreased fetal production of adrenocorticotrophic hormone (ACTH) and, in turn, the adrenal gland becomes less stimulated and suffers hypotrophy (FOWDEN et al, 2016; O'DONNELL et al, 2017).

The developing adrenal gland originates from two different embryonic layers: a mesodermal portion, which forms the cortex; and an ectodermal portion, which forms the medulla. During the fifth week of development, mesothelial cells, between the root of the mesentery and the developing gonad, begin to proliferate and penetrate the underlying mesenchyme differentiating into large acidophilic cells that form the fetal adrenal cortex

(MONTENEGRO YHA, 2019; SADLER, 2021). While the fetal cortex is being formed, neural crest cells invade its medial region, where they are arranged in strands and clusters to form the medulla of the gland. When differentiated, these cells are called chromaffin cells (SADLER, 2021). These cells represent modified postganglionic sympathetic neurons that are innervated by sympathetic fibers and, when stimulated, produce epinephrine and norepinephrine, which are released directly into the bloodstream (BUSADA; CIDLOWSKI, 2017; MONTENEGRO YHA, 2019).

The initiation of glucocorticoid production by the fetus is closely linked to the development of the adrenal gland. Hormone production is tightly controlled by the regional expression of a cascade of steroidogenic enzymes (BUSADA; CIDLOWSKI, 2017; BATTARBEE; YE; SZYCHOWSKI; CASEY; TITA; BOGGESS, 2022). Prolonged exposure to high levels of glucocorticoids suppresses fetal and placental growth and has been associated with cardiovascular disease, metabolic disorders, neurological and learning defects (MONTENEGRO YHA, 2019; O'DONNELL, 2017).

Alterations resulting from the increase of corticoids in the encephalic region also trigger changes in the cerebral cortex, besides alterations in neurotransmitters and synapses. In this sense, any interference during pregnancy, which implies in changes in the quantity of hormonal or teratogenic substances that reach this cortex, can modify the quantity of neurons, their connections and plasticity. The association between depressive symptoms and neuronal population indicates that cortical thinning is a proposed endophenotype for depression and mediates, in part, the relationship between prenatal maternal mood and externalizing behaviors (MORGADO et al, 2017).

When allocated in fetal metabolism, GRs are directed to their receptors in the prefrontal cortex and hippocampus, causing dendritic atrophy and synaptic loss, generating deficits in working memory, declarative memory, and behavioral flexibility. The loss of part of the functionality in the prefrontal cortex promotes hypertrophy of the terminal nucleus, which is directly related to anxious behavior (O'DONNELL, et al, 2017; MORGADO et al, 2017). Recent studies performed soon after birth reveal that prenatal maternal anxiety promotes variation in the microstructure of fetal brain regions important for emotional function, cognitive (right insula and dorsolateral prefrontal cortex), sensory processing (right middle occipital cortex) and social emotional function (right angular gyrus, uncinate fasciculus, posterior cingulum and parahippocampus), predicting infant internalizing behavior (CASULARI et al, 2022, O'DONNELL et al, 2017).

Moreover, birth weight is a risk marker for possible metabolic disorders that will accompany the individual in the future. The analysis of low birth weight exposes the intergenerational actions of glucocorticoids, which lead to obesity, hypertension, metabolic syndrome, cardiovascular disease, cognitive delays, and mental health deficits, manifested through increased susceptibility to develop schizophrenia, alcohol and drug use disorders, ADHD, anxiety disorders, and somatoform disorders in adulthood (O'DONNELL et al, 2017; FOWDEN, et al, 2016; BATTARBEE; YE; SZYCHOWSKI; CASEY; TITA; BOGGESS, 2022).

4.5 TDAH AND ITS RELATION

Attention deficit hyperactivity disorder (ADHD) is characterized as one of the psychiatric disorders that most commonly affects children, with a prevalence of 3 to 5%. (FORTIER et al, 2012; SCHOTE et al, 2016; NOORDERMEER; LUMAN; OOSTERLAAN, 2016). The significant heritability, from 70 to 80% of cases, shows the contribution of the genetic character in the etiopathogenesis of ADHD. In addition, gene-environment interactions may have an influence on dopamine receptors, the main focus of clinical investigations in ADHD (CHEN, 2019; GRAY et al, 2017; NOORDERMEER; LUMAN; OOSTERLAAN, 2016). In this sense, the dysregulation of the HPA axis, may contribute to the development of ADHD (FORTIER et al, 2012; SCHOTE et al, 2016).

Children with ADHD have a resistant cortisol response to psychosocial stressors, a decreased cortisol arousal response, or lower plasma daytime cortisol (CHEN, 2019; FORTIER et al, 2012). Although GR and MR are abundantly expressed in the brain, genetic variants of GR have direct effects on the functioning of neurons present in the prefrontal cortex, hippocampus and amygdala (WU, L.H., CHENG, W., YU, M. et al, 2017; SCHOTE et al, 2016; ZHU Y et al, 2020), which are often impaired in individuals with ADHD (MCEWEN; NASCA; GRAY, 2015; MEER et al, 2016; SCHOTE et al, 2016).

Because GR and MR mediate the cortisol signal, variations in the two genes encoding these receptors (NR3C1 and NR3C2) have been associated with four functional single nucleotide polymorphisms (SNPs) in NR3C1. Consequently, this polymorphism has stabilizing effects on the mRNA of the GR-9 haplotype (MEER et al, 2016; SCHOTE et al, 2016). Altered GR-9 gene expression is associated with higher serum cortisol levels. Furthermore, long-term exposure to stress can reduce NR3C1 expression, leading to reduced negative feedback from the HPA axis. This results in the reduction of GR activity to a pathologically low level, contributing to ADHD-related behavior. Furthermore, dexamethasone administration, increases

serotonin transporter gene (5-HTT) expression and its high availability is associated with lower NR3C1 expression. We therefore suggest the presence of a feedback loop between GR and 5-HTT, raising the possibility that genetic variation in NR3C1 and 5-HTT may moderate their effects on the stress response in the brain (MEER et al, 2016; SCHOTE et al, 2016). Also, glucocorticoids interact with other neurotransmitter systems in the brain, such as the monoaminergic neurotransmitter system, which has been shown to be involved in the pathogenesis of ADHD, such as dopamine (DA) and norepinephrine (NE), responsible for the biochemical mechanism of attention. ADHD sufferers have an imbalance in the concentration of available DA and NE in the brain synaptic cleft, also associated with dysfunction of the DA receptor in the brain (CHEN, 2019; CHEN, 2017; SCHOTE et al, 2016).

According to studies, there are also differences in the stress response in the metabolism of female and male offspring due to the fact that the enzyme 11βHSD2 is more highly expressed in the placenta of the female fetus (REYNOLDS, 2013; FOWDEN et al, 2016; LAUGESEN; BYRJALSEN; FROSLEV; OLSEN; SORENSEN, 2017). This may indicate why in boys this disorder is more prevalent (REYNOLDS, 2013; FOWDEN et al, 2016). However, it is important to remember that studies demonstrating how the influence of prenatal maternal habits modify the anatomical and functional characteristics of the fetus through medication, food, and external stressors are still lacking. Moreover, even with the discovery of neurotransmitters and genes responsible for cortical alteration and development of ADHD, new researches are still required to help explore the etiologies and risk factors of this disorder, thus contributing to improve future interventions and treatments.

5 CONCLUSION

The effects of overexposure to glucocorticoids, especially prednisolone and hydrocortisone, in early pregnancy cause changes in gene expression and structure of the HPA axis, which may persist throughout life or even into the subsequent generation. Thus, glucocorticoid-induced changes may become maladaptive and lead to the onset of neuronal dysfunctions, related to dendritic atrophy, synaptic loss in the prefrontal cortex and hippocampus, decreased dopamine concentration in the brain, leading to attention deficit hyperactivity disorder. Thus, glucocorticoids and their influences on metabolic programming remain a topic for discussion, as studies demonstrating how and why these neurotransmitters decrease and/or change are still lacking.

HIGHLIGHTS

1 - Epigenetic factors are involved in the modulation of the fetal brain, generating ADHD;

2 - Prednisolone and dexamethasone act as maternal villains in the first months of pregnancy;

3 - Increased cortisol reduces dopamine levels in the cerebral cortex.

4 - Decreased dopamine and increased noradrenaline in the prefrontal cortex results in ADHD.

REFERENCES

ALTARESCU A, CRAIG MC, GLOVER V. Prenatal stress: **Effects on fetal and child brain development. International Review of Neurobiology**. 2020 ;150:17-40. DOI: 10.1016/bs.irn.2019.11.002. PMID: 32204831.

BARBOSA, Ariadne. **Programação metabólica por exposição materna ao glifosato: avaliação morfológica dos músculos extensor longo dos dedos e sóleo de camundongos C57BL/6**. 2020. 95 f. Dissertação (Programa de Pós- Graduação em Biociências e Saúde) - Universidade Estadual do Oeste do Paraná, Cascavel - PR.

BATTARBEE AN, YE Y, SZYCHOWSKI JM, CASEY BM, TITA AT, BOGGESS KA. **Euglycemia after antenatal late preterm steroids: a multicenter, randomized controlled trial**. Am J Obstet Gynecol MFM. 2022 Jul;4(4):100625. doi: 10.1016/ j.ajogmf.2022.100625. Epub 2022 Mar 26. PMID: 35346889; PMCID: PMC9195161.

BAVARESCO, Luci; BERNARDI, Andressa; BATTASTINI, Ana Maria Oliveira. GLICOCORTICOIDES: USOS CLÁSSICOS E EMPREGO NO TRATAMENTO DO CÂNCER. **Infarma - Ciências Farmacêuticas**, [S.l.], v. 17, n. 7/9, p. 50-60, jan. 2013. ISSN 2318-9312. Disponível em: <http://www.revistas.cff.org.br/?journal=infarma&page=article&op=view&path%5B%5D=260>. Acesso em: 25 jan. 2022.

BEHURA SK, DHAKAL P, KELLEHER AM, BALBOULA A, PATTERSON A, SPENCER TE. **The brain-placental axis: Therapeutic and pharmacological relevancy to pregnancy.** Pharmacol Res. 2019 Nov;149:104468. doi: 10.1016/ j.phrs.2019.104468. Epub 2019 Oct 7.

BENZING, Valentin; SCHMIDT, Mirko. The effect of exergaming on executive functions in children with ADHD: a randomized clinical trial. **Scandinavian Journal Of Medicine & Science In Sports**, [S.L.], v. 29, n. 8, p. 1243-1253, 23 maio 2019. Wiley. http://dx.doi.org/10.1111/sms.13446.

BRUNTON, L. L. **As bases farmacológicas da terapêutica de Goodman e Gilman**. Porto Alegre: AMGH, 2018.

BUSADA, J. T., & CIDLOWSKI, J. A. (2017). ***Mechanisms of Glucocorticoid Action During Development. Nuclear Receptors in Development and Disease***, *147–170.* doi:10.1016/bs.ctdb.2016.12.

CAI, Emmy; CZUZOJ-SHULMAN, Nicolas e ABENHAIM, Haim A. Maternal and fetal outcomes in pregnancies with long-term corticosteroid use, **The Journal of Maternal-Fetal & Neonatal Medicine**, 34:11, 1797-1804; 2021. DOI: 10.1080/14767058.2019.1649392

CASTRO, María J. Programación fetal. **Revista Digital de Postgrado**, Caracas, v. 9, n. 2, p. 1-14, ago. 2020. Disponível em: https://pesquisa.bvsalud.org/portal/ resource/pt/biblio-1103446. Acesso em: 10 dez. 2021.

CASULARI, Luiz Augusto; MOTTA, Lucilia Casulari da. Antenatal corticosteroids may contribute to illness in children in the future. **Arch. Endocrinol. Metab.**, São Paulo , v. 66, n. 1, p. 129-131, Feb. 2022 . Available from <http://old.scielo.br/scielo.php?script=sci_arttext&pid=S2359-39972022000100129&lng=en&nrm=iso>. access on 30 Apr. 2022. Epub Mar 16, 2022. https://doi.org/ 10.20945/2359-3997000000434.

CHEN, X., Wang, M., Zhang, Q., Hou, Y., Huang, X., Li, S., & Wu, J. (2019). ***Stress response genes associated with attention deficit hyperactivity disorder****: a case-control study in Chinese children. Behavioural Brain Research.* doi:10.1016/ j.bbr.2019.01.

CHEN, Yanhui; ZHENG, Xiaolan; XIE, Linqi; HUANG, Liang; KE, Zhongling; ZHENG, Jie; LU, Hongzhu; HU, Jun. Glucocorticoids/glucocorticoid receptors effect on dopaminergic neurotransmitters in ADHD rats. **Brain Research Bulletin**, [S.L.], v. 131, p. 214-220, maio 2017. Elsevier BV. http://dx.doi.org/10.1016/j.brainresbull. 2017.04.013.

COSTA, Débora Bomfim; COELHO, Helena Lutescia Luna; SANTOS, Djanilson Barbosa dos. **Utilização de medicamentos antes e durante a gestação: prevalência e fatores associados**. Cad. Saúde Pública, Rio de Janeiro , v. 33, n. 2, e00126215, 2017 . Disponível em <http://www.scielo.br/scielo.php? script=sci_arttext&pid=S0102-311X2017000205005&lng=pt&nrm=iso>. acessos em 15 mar. 2021. Epub 09-Mar-2017. https://doi.org/10.1590/0102-311x00126215.

CUTOLO M, LACCARINO L, DORIA A, GOVONI M, SULLI A, MARCASSA C. **Efficacy of the switch to modified-release prednisone in rheumatoid arthritis patients treated with standard glucocorticoids.** Clin Exp Rheumatol. 2013 Jul- Aug;31(4):498-505. Epub 2013 Feb 15. PMID: 23415134.

FALL, Caroline H. D.; KUMARAN, Kalyanaraman. Metabolic programming in early life in humans. **Philos Trans R Soc Lond B Biol Sci**, London, v. 1, p. 374-383, 15 abr. 2019. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6460078/. Acesso em: 15 ago. 2021.

FORTIER, Marie-Ève; SENGUPTA, Sarojini M.; GRIZENKO, Natalie; CHOUDHRY, Zia; THAKUR, Geeta; JOOBER, Ridha. Genetic Evidence for the Association of the Hypothalamic–Pituitary–Adrenal (HPA) Axis with ADHD and Methylphenidate Treatment Response. **Neuromolecular Medicine**, [S.L.], v. 15, n. 1, p. 122-132, 10 out. 2012. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/ s12017-012-8202-1.

FOWDEN, A.L.; VALENZUELA, O.A.; VAUGHAN, O.R.; JELLYMAN, J.K.; FORHEAD, A.J.. Glucocorticoid programming of intrauterine development. **Domestic Animal Endocrinology**, [S.L.], v. 56, n. 8, p. 121-132, jul. 2016. Elsevier BV. http://dx.doi.org/10.1016/j.domaniend.2016.02.014.

GJERSTAD, Julia K; LIGHTMAN, Stafford L; SPIGA, Francesca. Role of glucocorticoid negative feedback in the regulation of HPA axis pulsatility. **Taylor and Francis**, Bristol, v. 5, n. 1, p. 403-416, 15 maio 2018. Disponível em: https:// www.tandfonline.com/doi/full/10.1080/10253890.2018.1470238. Acesso em: 11 mar. 2022.

GLOVER, V., O'DONNELL, K., O'CONNOR, T., & FISHER, J. (2018). **Prenatal maternal stress, fetal programming, and mechanisms underlying later psychopathology—A global perspective**. *Development and Psychopathology*, *30*(3), 843-854. doi:10.1017/S095457941800038X

GRAY, J., KOGAN, J., MARROCCO, J. *et ai.* Mecanismos genômicos e epigenômicos dos glicocorticoides no cérebro. ***Nat Rev Endocrinol*** 13, 661-673 (2017). https://doi.org/10.1038/nrendo.2017.97

HANC Tomasz, CORTESE Samuele, Attention deficit/hyperactivity-disorder and obesity: A review and model of current hypotheses explaining their comorbidity, **Neuroscience & Biobehavioral Reviews**, Volume 92, 2018, Pages 16-28, ISSN 0149-7634, https://doi.org/10.1016/j.neubiorev.2018.05.017.

HERMAN, James P.; MCKLVEEN, Jessica M.; GHOSAL, Sriparna; KOPP, Brittany; WULSIN, Aynara; MAKINSON, Ryan; SCHEIMANN, Jessie; MYERS, Brent. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. **Comprehensive Physiology**, [S.L.], p. 603-621, 15 mar. 2016. Wiley. http:// dx.doi.org/10.1002/cphy.c150015.

KATZUNG, B. **Farmacologia básica e clínica**. Porto Alegre: AMGH, 2017. ISBN 9788580555967. Disponível em: https://search.ebscohost.com/login.aspx?direct=true&db=edsmib&AN=edsmib.000011541&lang=pt-br&site=eds-live. Acesso em: 10 jan. 2021.

LAUGESEN, Kristina; BYRJALSEN, Anna; FRØSLEV, Trine; OLSEN, Morten s; SØRENSEN, Henrik Toft. **Use of glucocorticoids during pregnancy and risk of attention-deficit/hyperactivity disorder in offspring: a nationwide danish cohort study.** Bmj Open, [S.L.], v. 7, n. 9, p. 016825, set. 2017. BMJ. http://dx.doi.org/ 10.1136/bmjopen-2017-016825.

LESTER, BARRY M and CARMEN, J Marsit. **"Epigenetic mechanisms in the placenta related to infant neurodevelopment."** *Epigenomics* vol. 10,3 (2018): 321-333. doi:10.2217/epi-2016-0171

LIMA TELES DA HORA, A.; SILVA, S.; RAMOS, M.; PONTES, F.; NOBRE, J. A prevalência do transtorno do déficit de atenção e hiperatividade (tdah): Uma revisão de literatura. **PSICOLOGIA**, v. 29, n. 2, p. 47-62, 1 dez. 2015.

LONGUI, Carlos Alberto. Corticoterapia: minimizando efeitos colaterais. **Sociedade Brasileira de Pediatria: Jornal de Pediatria.** Rio de Janeiro, p. 163-171. nov. 2007. Disponível em: https://www.scielo.br/j/jped/a/fjqmm8pXQSkrqPGRnk6TTgD/? lang=pt#. Acesso em: 18 jan. 2022.

M.D. Lockshin; L.R. Sammaritano. Corticosteroids during pregnancy, **Scandinavian Journal of Rheumatology**, 27:sup107, 136-138; 2016. DOI: 10.1080/03009742.1998.11720789

MARCINIAK, Aleksandra; PATRO-MAŁYSZA, Jolanta; KIMBER-TROJNAR, Żaneta; MARCINIAK, Beata; OLESZCZUK, Jan; LESZCZYńSKA-GORZELAK, Bożena. **Programação fetal da síndrome metabólica**. Lublin: Elsevier, 2017. 133-138 p. Disponível em: https://www.sciencedirect.com/science/article/pii/ S1028455917300025?via%3Dihub. Acesso em: 15 dez. 2021.

MCEWEN, Bruce s; NASCA, Carla; GRAY, Jason D. Stress Effects on Neuronal Structure: hippocampus, amygdala, and prefrontal cortex. **Neuropsychopharmacology**, [S.L.], v. 41, n. 1, p. 3-23, 16 jun. 2015. Springer Science and Business Media LLC. http://dx.doi.org/10.1038/npp.2015.171.

MEER, D. van Der; HOEKSTRA, P. J.; BRALTEN, J.; VAN DONKELAAR, M.; HESLENFELD, D. J.; OOSTERLAAN, J.; FARAONE, S. V.; FRANKE, B.;

BUITELAAR, J. K.; HARTMAN, C. A.. Interplay between stress response genes associated with attention-deficit hyperactivity disorder and brain volume. **Genes, Brain And Behavior**, [S.L.], v. 15, n. 7, p. 627-636, 3 ago. 2016. Wiley. http:// dx.doi.org/10.1111/gbb.12307.

MONTENEGRO YHA, de QUEIROGA NASCIMENTO D, de ASSIS TO, Santos- Lopes SSD. **The epigenetics of the hypothalamic-pituitary-adrenal axis in fetal development.** Ann Hum Genet. 2019 Jul;83(4):195-213. doi: 10.1111/ahg.12306. Epub 2019 Mar 7. PMID: 30843189.

MORGADO, Pedro *et al*. Resposta Neuronal ao Stress. In: MINHO, Universidade do. **Instituto de Investigação em Ciências da Vida e Saúde (ICVS)**. Braga: Lidel - Edições Técnicas, 2017. p. 1-18. Disponível em: http://repositorium.sdum.uminho.pt/ handle/1822/50828. Acesso em: 17 abr. 2022.

NAKAI T, KITADA A, FUKUI S, OKADA M. **Risk of adverse pregnancy outcomes in Japanese systemic lupus erythematosus patients with prior severe organ manifestations: A single-center retrospective analysis.** Lupus. 2021 Aug;30(9): 1415-1426. doi: 10.1177/09612033211016074. Epub 2021 May 20. PMID: 34013819.

NOORDERMEER, Siri D. S.; LUMAN, Marjolein; OOSTERLAAN, Jaap. **A Systematic Review and Meta-analysis of Neuroimaging in Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) Taking Attention-Deficit Hyperactivity Disorder (ADHD) Into Account.** Neuropsychology Review, [S.L.], v. 26, n. 1, p. 44-72, 5 fev. 2016. Springer Science and Business Media LLC. http:// dx.doi.org/10.1007/s11065-015-9315-8.

NORONHA, Gisele Almeida de; KALE, Pauline Lorena; TORRES, Tania Zdenka Guillén de; COSTA, Antonio Jose Leal; CAVALCANTI, Maria de Lourdes Tavares; SZKLO, Moyses. Validade da informação sobre o peso ao nascer para estudos fundamentados na programação fetal. **Caderno de Saúde Pública**, Rio de Janeiro, v. 1, n. 7, p. 1-12, 10 jul. 2017. Disponível em: https://www.scielo.br/j/csp/a/ hvWrXHm3by7YZyx3mdT4XYB/?lang=pt. Acesso em: 17 ago. 2021.

O'DONNELL, Kieran J.; MEANEY, Michael J.. Fetal Origins of Mental Health: the developmental origins of health and disease hypothesis. **American Journal Of Psychiatry**, [S.L.], v. 174, n. 4, p. 319-328, abr. 2017. American Psychiatric Association Publishing. http://dx.doi.org/10.1176/appi.ajp.2016.16020138.

OWEN, D., Andrews, M. H., & Matthews, S. G. (2005). RETRATADO: **Adversidade materna, glicocorticoides e programação da função e comportamento neuroendócrino**. Neuroscience & Biobehavioral Reviews, 29 (2), 209–226. doi: 10.1016 / j.neubiorev.2004.10.

OYOLA MG, Handa RJ. **Hypothalamic-pituitary-adrenal and hypothalamic- pituitary-gonadal axes: sex differences in regulation of stress responsivity**. Stress. 2017 Sep;20(5):476-494. doi: 10.1080/10253890.2017.1369523. Epub 2017 Aug 31. PMID: 28859530; PMCID: PMC5815295.

PATRICK O McGowan, STEPHEN G Matthews, **Prenatal Stress, Glucocorticoids, and Developmental Programming of the Stress Response*, Endocrinology***, Volume 159, Issue 1, January 2018, Pages 69–82, https://doi.org/10.1210/en. 2017-00896

PAULINO, Jéssica *et al*. **Uso indiscriminado de glicocorticoides e sua consequencia fetal durante a gestação.** 2021. 8 f. TCC (Graduação) - Curso de Farmácia, Univag, Várzea Grande, 2021. Disponível em: https:// www.repositoriodigital.univag.com.br/index.php/far/article/view/663. Acesso em: 17 jan. 2022.

PEARSON, Jessica; TARABULSY, George M.; BUSSIÈRES, Eve-Line. Foetal programming and cortisol secretion in early childhood: a meta-analysis of different programming variables. **Infant Behavior And Development**, [S.L.], v. 40, p. 204-215, ago. 2015. Elsevier BV. http://dx.doi.org/10.1016/j.infbeh.2015.04.004.

PERRONE S, SANTACROCE A, PICARDI A, BUONOCORE G. Fetal programming and early identification of newborns at high risk of free radical-mediated diseases. ***World J Clin Pediatr*** 2016; 5(2): 172-181 [PMID: 27170927 DOI: 10.5409/ wjcp.v5.i2.172]

REYNOLDS, Rebecca M.. Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis ⁖ 2012 curt richter award winner. **Psychoneuroendocrinology**, [S.L.], v. 38, n. 1, p. 1-11, jan. 2013. Elsevier BV. http://dx.doi.org/10.1016/j.psyneuen.2012.08.012.

RIBEIRO, Alinne Souza et al. RISCO POTENCIAL DO USO DE MEDICAMENTOS DURANTE A GRAVIDEZ E A LACTAÇÃO.**Infarma - Ciências Farmacêuticas**, [S.l.], v. 25, n. 1, p. 62-67, apr. 2013. ISSN 2318-9312. Disponível em: <http:// revistas.cff.org.br/?journal=infarma&page=article&op=view&path%5B%5D=441>. Acesso em: 25 jan. 2022. doi:http://dx.doi.org/ 10.14450/2318-9312.v25.e1.a2013.pp62-67.

POLDERMAN JA, FARHANG-RAZI V, VAN DIEREN S, KRANKE P, DEVRIES JH, HOLLMANN MW, PRECKEL B, HERMANIDES J. Adverse side effects of dexamethasone in surgical patients. **Cochrane Database Syst Rev.** 2018 Nov 23;11(11):CD011940. doi: 10.1002/14651858.CD011940.pub3. PMID: 30480776; PMCID: PMC6426282.

ROLDÃO, Carolina Fidalgo da Cruz. **Leite materno e programação metabólica: benefícios para a saúde a curto e a longo prazo**. 2019. 35 f. Dissertação (Mestrado) - Curso de Medicina, Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, 2019. Disponível em: https://repositorio-aberto.up.pt/bitstream/ 10216/121296/2/343878.pdf. Acesso em: 22 dez. 2021.

SACCONE, Gabriele; BERGHELLA, Vincenzo. **Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials.** Bmj, [S.L.], p. 5044, 12 out. 2016. BMJ. http:// dx.doi.org/10.1136/bmj.i5044.

SADLER, T. W. **Langman Embriologia médica**. Rio de Janeiro: Guanabara Koogan, 2021. ISBN 9788527736022. Disponível em: https://search.ebscohost.com/ login.aspx?direct=true&db=edsmib&AN=edsmib.000020926&lang=pt-br&site=eds- live. Acesso em: 9 mar. 2022.

SAÚDE, Ministério da. **Gestação de Alto Risco**. 5. ed. Brasília: Editora Ms, 2012. 302 p. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/ manual_tecnico_gestacao_alto_risco.pdf. Acesso em: 20 jan. 2022.

SCHOTE, Andrea B.; BONENBERGER, Martina; PÁLMASON, Haukur; SEITZ, Christiane; MEYER, Jobst; FREITAG, Christine M.. Glucocorticoid receptor variants in childhood attention-deficit/hyperactivity disorder and comorbid psychiatric disorders. **Psychiatry Research**, [S.L.], v. 246, p. 275-283, dez. 2016. Elsevier BV. http://dx.doi.org/10.1016/j.psychres.2016.10.001.

SIQUEIRA, Marcelo Martins; FARIA, Talitha Araújo. **Efeitos Colaterais no Organismo Humano no uso de Glicocorticoides**. Sete Lagoas: Uniatenas, 2017. Disponível em: http://www.atenas.edu.br/uniatenas/assets/files/magazines/ EFEITOS_COLATERAIS_NO_ORGANISMO_HUMANO_NO_USO_DE_GLICOCOR TICOIDES.pdf. Acesso em: 20 jan. 2022

TAVARES, F. R. S. .; LUZ , E. R. da .; SILVA, C. E. G. da .; CARVALHO , J. M. . L. de B. .; SOUSA, A. P. de .; FERREIRA, M. D. L. . Deleterious effects of chronic use of corticosteroids: an approach to the development of Cushing's Syndrome. **Research, Society and Development**, *[S. l.]*, v. 10, n. 4, p. e12310413487, 2021. DOI: 10.33448/rsd-v10i4.13487. Disponível em: https://rsdjournal.org/index.php/rsd/ article/view/13487. Acesso em: 10 fev. 2022.

WU, L.H., CHENG, W., YU, M. *et al.* Nr3C1-Bhlhb2 Axis Dysregulation Is Involved in the Development of Attention Deficit Hyperactivity. ***Mol Neurobiol*** **54**, 1196–1212 (2017). https://doi.org/10.1007/s12035-015-9679-z

XIONG, Fuxia; ZHANG, Lubo. Role of the hypothalamic–pituitary–adrenal axis in developmental programming of health and disease. **Frontiers In**

Neuroendocrinology, [S.L.], v. 34, n. 1, p. 27-46, jan. 2013. Elsevier BV. http:// dx.doi.org/10.1016/j.yfrne.2012.11.002.

ZHU Y, WANG Y, YANG Z, WANG L, HU X. **Endogenous cortisol-related alterations of right anterior insula functional connectivity under acute stress.** J Affect Disord. 2020 Sep 1;274:231-238. doi: 10.1016/j.jad.2020.05.123. Epub 2020 May 23. PMID: 32469811.