Chapter 17

Glucocorticoids: Biochemical Group That Play Key Role in Fetal Programming of Adult Disease

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Glucocorticoids discovery started 160 years ago

Glucocorticoids are subclass from corticosteroids. The other subclass of corticosteroids is mineralocorticoids. Historically, the discovery of glucocorticoids has been commenced during the early of last century. In fact, glucocorticoids have revealed themselves by their absence. In 1849, Thomas Addison, who was a physician at Guy`s Hospital in London, had noticed that certain patients were presenting with a cluster of characteristic clinical picture including anemia, weakness, peculiar dark skin color and eventually death (1). He presented his observation on 11 cases at the South London medical society meeting. In 1855 he published monograph entitled (On the Constitutional and Local Effects of Disease of the Supra-Renal capsules), (2, 3). 100 years later, Dr Philip Hench with a collaborated work with Edward Kendall, Professor of Physiological Chemistry, were both at Mayo Clinic which was first rheumatic disease service, had extracted "substance X" and in 21 September 1948 first injection of substance X was given to 29 years old lady who was suffering from severe, erosive arthropathies and became able to walk out of the hospital after 4 days of treatment. Dr Hench then named substance X Cortisone and shared the Nobel prize with professor Kendall in 1950 (4).

1.2. Glucocorticoids characteristics

Glucocorticoids (GCs) are belonging to the steroid group of the hormones that bind to the glucocorticoid receptor, which is present in almost all cells (5). This is the reason why the GCs play wide range of vital physiological roles in the human and other vertebrate bodies (6, 7). They play pivotal role in modulation and regulation of metabolism (8), immune system reaction (9, 10) and more significantly they are essential for normal development and cognition (11).

1.2.1. Biochemical characteristics

To know how GCs exerts their wide range effects, it is crucial to know about their structure and the synthesis pathway. GCs are one of the steroid hormones group. All steroid hormones are derived from cholesterol. These include: sex hormones (Testosterone, estrone (E1), estradiol (E2), estriol (E3), and progesterone) adrenal cortex hormones (Cortisone, the main glucocorticoid and Aldosterone, the main mineralocorticoid) in addition to vitamin D. It is essential to know that androgens are the synthetic precursors of estrogens which mediated mainly by a specific cytochrome P 450 enzyme named aromatase. Each one of these steroid hormones can be a product and precursor in the same time. This is the reason why any defect in the synthesis of one steroid hormone will lead to derangement in the synthesis of the other hormones. For instance, in congenital adrenal hyperplasia (CAH), an autosomal recessive gene defect of the enzyme 21-hydroxylase, there will be blocked synthesis of aldosterone and cortisol pathways. Subsequently, all precursors will be directed toward androgenic pathway which does not involve 21-hydroxylation and eventually lead to excess production of androgens (Figure 1). Fetus with this congenital disease will be exposed to high levels of androgens as early as 3 months of gestation and hence during a critical window of sexual differentiation. As a result a female fetus will develop an ambiguous genitalia or male external genitalia under the influences of adrenal androgens. However, this is associated with varying degrees of GCs and mineralocorticoids deficiencies. In severe cases there will be salt wasting with low sodium and potassium in serum due to aldosterone deficiency (12). Currently, all neonates in the most of world are screened for CAH by measuring 17-Hydroxyprogesteron (17-OHP) in filter-paper blood samples at week one of life. An elevated 17-OHP indicated affected baby. Recently, there are promising clinical trials in prenatal diagnosis and treatments of such condition by giving the mother dexamethasone injections to prevent increased secretion of Adreno-Cortico-Tropic Hormone (ACTH) and subsequently adrenal androgens(13-17).

1.2.2. Physiological characteristics

GCs are needed mainly for energy where as mineralocorticoids are needed for mineral balance. GCs regulates wide range of cellular, molecular and the physiological processes in human body that are crucial for life such as growth, reproduction, essential metabolism, immune responses and inflammatory reactions, as well as central nervous system and cardiovascular functions (19-22). For all these roles to be achieved, adrenal GCs is considered as a ring which coupled with many other rings to form an integrated chain that acts in coordination, this chain is the hypothalamus-pituitary- adrenal axis.

1.2.2.1. Hypothalamus-pituitary-adrenal axis (HPA axis)

HPA axis serves as a master that controls major body systems and is considered as a main connecting pathway between central nervous system and endocrine system. It regulates majority of physiological function as well as it maintains homeostasis in acute stress. In the later situation, the brain will signal the stress to the paraventricular nucleus (PVN) in the hypothalamus which eventually secretes corticotrophin releasing hormone (CRH). CRH is

then transported through hypophyseal portal system to the pituitary gland and induces the conversion of pro-opiomelanocortin into ACTH as well as its secretion from anterior pituitary to the systemic circulation. ACTH is the primary regulator of adrenal cortical steroidogenesis. ACTH will induce the synthesis of adrenal steroids (GCs and androgens) in zonae fasciculate and reticularis of adrenal cortex (Figure 1). The ACTH itself is under the influences of negative feedback inhibition which exerted by the plasma levels of circulating free GCs (Figure 2).

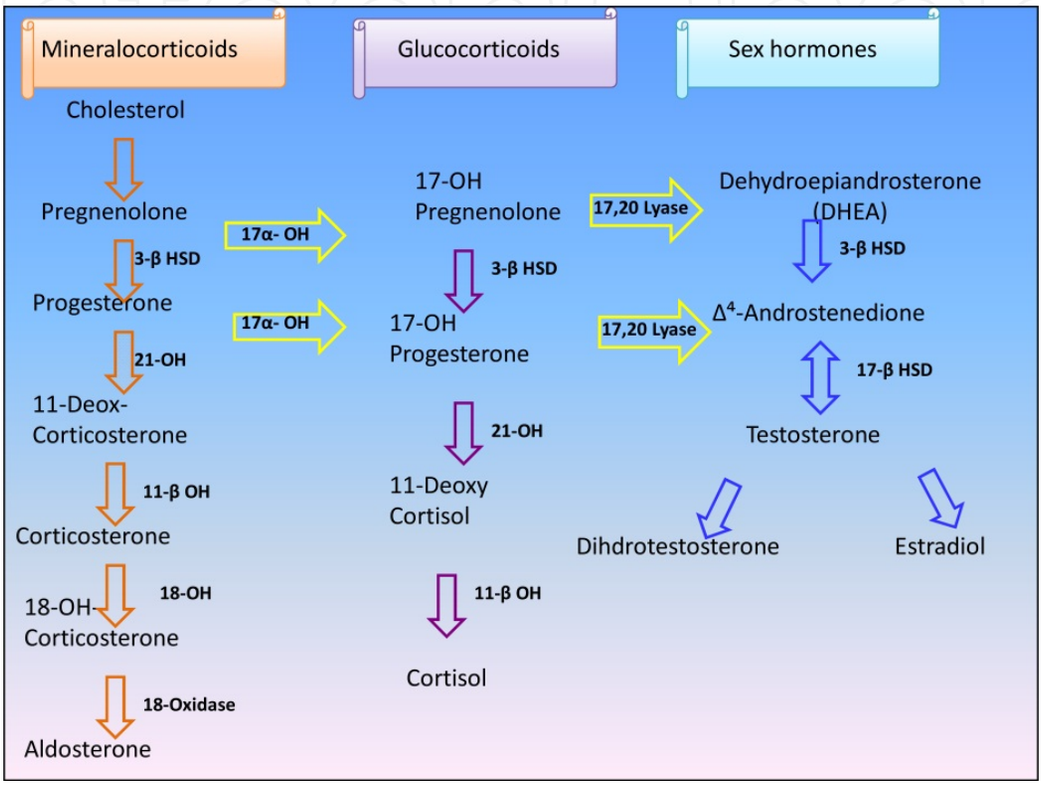

Figure 1. Adrenal gland steroidogenesis. The synthesis of adrenal steroids is started by transfer of cholesterol either from blood or from adrenal gland lipid droplets into mitochondria where it will be converted to pregnenolone. In zona glomerulosa pregnenolone will be hydroxylated to corticosterone and further oxidized to aldosterone where as in zona fasciculate and zona reticularis it will be hydoxylated to cortisol or undergoes cleavage to form the main adrenal androgen (DHEA). HSD: Hydroxysteroid Dehydrogenase, OH: Hydroxylase, (18). Adrenal androgen synthesis is increased about age of 8 years, independent of gonads and puberty, and responsible for pubic and axillary hair growth and termed adrenarche.

1.2.2.2. Molecular mechanisms of GCs action

GCs secretion from zona fasciculata up on ACTH stimulation is not a continuance process but rather in a specific pattern known as circadian rhythm. Once GCs in circulation, 95% of them will be bound to a carrier proteins: 80–90% to corticosteroid binding globulin (CBG) and 10–15% to albumin, leaving only about 5% as active unbound cortisol (23). The free cortisol is the one which mediates the biological effect of GCs since it is able to diffuse through the cell membrane freely. The GCs are metabolized in liver by reduction followed by conjugation rendering them water soluble and ready for renal excretion in urine. Both

liver and kidney contain the enzyme 11 β-Hydroxysteroid dehydrogenase (11 β-HSD).There is two isoforms of this enzyme which catalyzes the opposite reactions. 11 β-Hydroxysteroid Dehydrogenase-2 (11 β-HSD 2) will inactivate the cortisol by converting it into cortisone. The 11 β-Hydroxysteroid dehydrogenase-1 (11 β-HSD 1) will convert inactive cortisone into cortisol. The net result will determine the plasma level of active cortisol in the body (24).

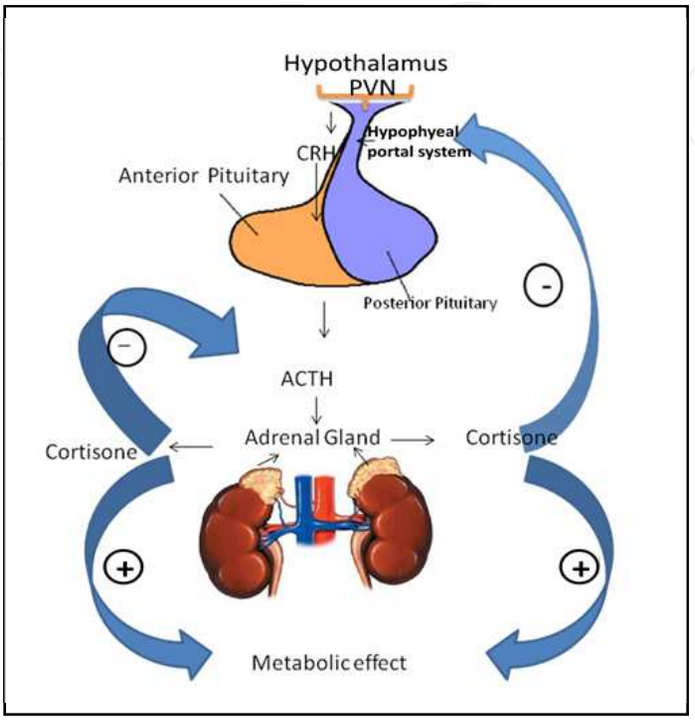

Figure 2. Schematic representation of Hypothalamic-pituitary-adrenal axis. PVN: Paraventricular nucleus, CRH: Corticotrophin releasing hormone, ACTH: Adrenocorticotropic hormone, ⊖: Inhibition, ⊕:Stimulation

Once free GCs defused through the plasma membrane of the target cell they will bind to intra-cytoplasmic receptors called glucocorticoids receptor (GR). GR-GCs complex will be now translocated to the nucleus and bind to glucocorticoids responsive elements (GRE) in the promoter of the target gene (Figure 3).

Human GR is 94 kDa protein which belongs to nuclear receptors known as Steroid/Thyroid/Retinoic acid superfamily and characterizing by being a ligand-dependent transcription factors that induce or suppress target gene expression (25). GCs are also able to alter gene expression of target genes independently to DNA-binding, but through interaction with other transcription factors, such as nuclear factor- κB, activator protein-1, p53 and signal transducers and activators of transcription (25).

Interestingly, there are two isoforms of GR, alpha (α) and beta (β) (26, 27). The GR-α is the one which is able to bind with glucocorticoids and subsequently to the GCs responsive element (GRE) of the DNA promoter region on the target gene. However, GR-β has no such ability to bind to GCs but its main role thought to be inhibitory to GR-α action by competitive interference on the GRE target sites (28). It has been found that the variations in

expression of GR-β is responsible for tissue sensitivity and resistance to GCs. Clinically, pathological conditions such as hypertension, rheumatoid arthritis, systemic lupus erythmatosis, ischemic heart disease and nasal carriage of Staphylococcus aureus are all associated with GR-β protein over-expression (29).

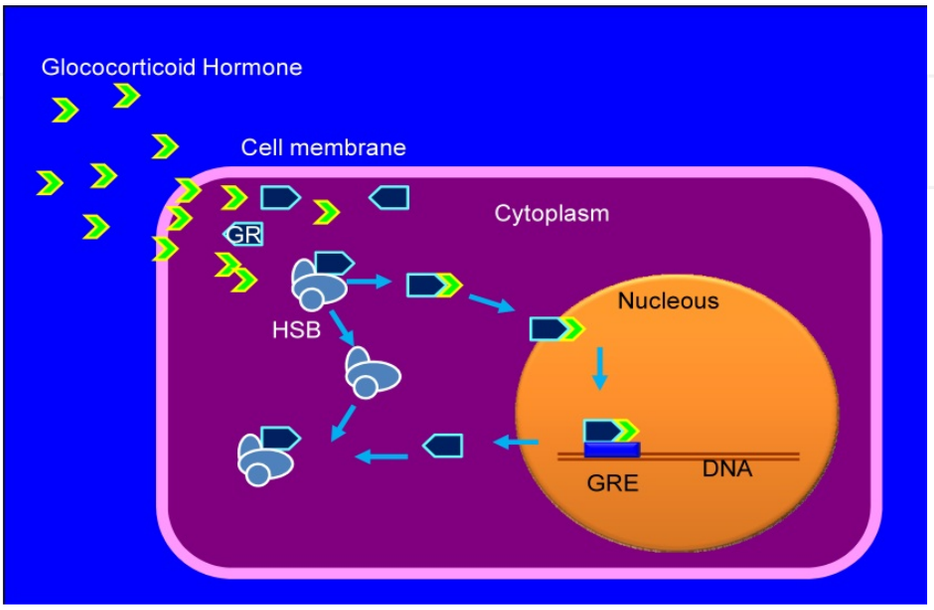

Figure 3. Representation of how glucocorticoid hormone enters to the cell and bind to intracellular glucocorticoids receptors (GR). Up on binding to GR they dissociate from heat shock proteins (HSP). The glucocorticoids-receptor complex enters the nucleus and bind to glucocorticoids responsive element (GRE) in the promoter of the responsive gene (25). Lastly, GR exit nucleus and recycled along with the HSP in the cytoplasm.

2. Tissue responses to glucocorticoids

As mentioned earlier that GR exist in almost every human cell, then we should not get surprised to observe the profound molecular, cellular, metabolic and other known biological events modulation in response to GCs excess or deficiency. Notwithstanding, for more understanding of these complex relationship and the huge difference in the treatment-response equation we categorized the human tissue into adult or mature human tissue and fetal or immature human tissue.

2.1. Adult (mature) tissue response to glucocorticoids

Adult cells and tissue characterized by being fully differentiated and mature. Therefore, influences will mainly affect their function.

2.1.1. Immune system

It is well established that the first medical use of GCs 60 years ago was for inflammation and autoimmune disease (30). GCs have significant influences on both cellular and humeral

immunity. They induce plasma cell immunoglobuline production and secretion and hence enhance humeral immunity (31). With regard to cellular immunity, GCs induce T-cell lymphocytosis (32), basophil apoptosis and neutrophilia by increasing bone marrow release of polymorphic neutrophils and decrease their migration to the inflammatory site (33, 34). Moreover, GCs enhances the phagocytosis and hence maximize the tissue clearance ability of the microorganisms and foreign antigens (35). It has been recently revealed that GCs can exert their immune-function manipulation at gene expression level. Galon and colleagues found that GCs significantly suppress the proinflamatory cytokines (IL1b, TNFa, IL-6, IL-8, IL- 12, IL-18) and chemokines gene expression where as the gene expression of anti-inflammatory cytokines (IL-10 and TGFb) are up-regulated (22).

2.1.2. Musculoskeletal system

It is known, from long history of GCs use, that prolonged high doses of GCs results in bone mineralization depletion with subsequent osteoporosis (36). As a result bone formation will be decreased and resorption will be increased (37-41). Bone loss occur in the first few months of treatment and can be improved after cessation of treatment (42-44). Importantly, the GCs induced-osteoporosis can be prevented by calcium and vitamin D supplementation along with GCs treatment course (45). GCs will also cause proximal myopathy which is dose dependent and again improves with discontinuation of treatment (46). GCs treatment increases the risk of femoral head avascular necrosis through a not well established mechanism, although some preliminary evidence pointing to venous endothelial injury (47, 48).

2.1.3. Vascular system

Use of GCs is associated with increased risk of ischemic heart disease and heart failure by increasing the occurrence of hypertension, hyperglycemia, dyslipideamia and obesity (49, 50). Rapid GCs infusion especially in patients with renal and cardiac co-morbidity was associated with sudden death (51).

2.1.4. Serum lipid levels

There are conflicting results from different studies regarding GCs induced hyperlipideamia. Berg and Nilsson-Ehle found that GCs may induce hyperlipideamia through ACTH suppression (52). Whereas others found that GCs may induce favorable lipid profiles in patients aged 60 years or more (53).

2.1.5. Serum glucose levels

GCs are considered diabetogenic hormones. Patients receiving therapeutic doses of GCs will have deranged plasma glucose level and even frank diabetes in glucose intolerant individuals (54, 55). The GCs-induced hyperglycemia is mainly due to reduced glucose peripheral disposal along with increased hepatic gluconeogenesis (56).

2.1.6. Central nervous system

Prolonged use of high doses of GCs is associated with marked behavioral and cognitive deficits. These disorders are more prevalent in those who have risk factors such as pre-existing psychiatric disorders, family history of depression or alcoholism (57). These disturbances are ranging from sleeping disturbances, insomnia, to hypomania, depression and psychosis (58) as well as memory disturbances (59). Recently, more evidences are accumulated to affirm the relationship between exposure to high GCs and impaired cognition. Ioannis and others found that chronic stress, through high endogenous GCs, precipitate cognitive impairment and Alzheimer's like disease (60).

2.1.7. Gastrointestinal system

Gastritis, peptic ulceration, and gastrointestinal hemorrhage all have been found to complicate GCs therapy especially if non-steroidal anti-inflammatory drugs are used concomitantly (61). Although, Chrousos and collegues indicated that GCs therapy could be related to acute pancreatitis in GCs user (62), but more recent studies have proven the opposite that GCs are not an etiological factor (63).

2.2. Fetal (Immature) tissue responses to glucocorticoids

Human intrauterine development is divided mainly into three stages: Zygote, from fertilization to implantation, embryo, from implantation to 8 weeks and fetus, from 8 weeks till term. The embryo and fetal tissues are characterized by rapid division and growth rendering them very susceptible to environmental influences and easily adaptive.

2.2.1. Short term effects of GCs over exposure in fetal life

2.2.1.1. Fetal over exposure to endogenous GCS

Fetal plasma GCs are mainly of maternal adrenal origin (64). This is essentially because of the biochemical, "partial" barrier role played by the placenta. The placenta contains the enzyme 11 β-HSD 2 which is responsible for inactivation of maternal cortisol into cortisone (Section 1.2.2) and hence maintains a normal feto-maternal concentration gradient of the hormone (65). This concentration gradient is species specific where it reaches 180 ng/ml in human; it is only 2 and 15 ng/ml in sheep and pig respectively (66). Therefore, we can assume that fetal exposure to maternal GCs is, at least partly, dependent on the placental activity of this enzyme. This is supported by the finding that in human umbilical cord blood cortisone/cortisol ratio, as a marker of placental 11 β-HSD 2, and the enzyme activity itself and its mRNA expression were lower in human pregnancies which complicated by intrauterine growth restriction (IUGR) (67) and each unit increase in cortisol/cortisone ratio was found to be associated with 1.6 mm Hg higher systolic blood pressure at 3 years of age (68).

GCs are essential for optimal fetal tissue maturation. GR are expressed in brain (69) where it is essential for development of neurons, the building unit in CNS, as well as the formation of

synapses by facilitating cortisone-induced axons and dendrites remodeling and neurons myelination (70). Human nervous system development during fetal life is a complex process where extensive proliferation of neurons occurs after initial migration between week 8 and 16 of gestation (71) to reach, at 28 weeks, approximately 40 % higher than total number of neurons in adult (72). These enormous numbers of neurons start to be connected by an extensive network of synapses where between 24 and 34 weeks of gestation more that 10,000 new synapses per second are formed (73). Therefore, exposure to altered plasma level of cortisone during these stages of development and vulnerability is able to alter the basic structure and subsequently the function of the CNS (74). The Maternal and fetal HPA axis are independent (Figure 4) where maternal cortisol is prevented to enter fetal compartment by placental 11 β-HSD 2 until late gestation where placental enzyme drops sharply and allow high levels of maternal free cortisol to enhance fetal lung, CNS and other tissue maturation (75). However, the placenta secretes placental corticotrophin releasing hormone (P-CRH) which is the major, if not the only, mean of cross talk between maternal and fetal HPA axis. As mentioned earlier (Section 1.2.2) that maternal cortisol is exerting negative feedback inhibition on her hypothalamus release of CRH, on contrast, it induces P-CRH secretion as pregnancy advances (76) which in turn will increase maternal and fetal adrenal cortisol secretion (77, 78).

Therefore, maternal either biological stress, like nutritional deprivation, immune reaction, hypertension, or psychological stress will be associated with high maternal cortisol and P-CRH which disrupt fetal nervous system development and affect postnatal cognitive and neuromuscular function. High P-CRH, as a marker of maternal stress, during third trimester associated with weak fetal responsiveness to noval stimuli (79). Postnataly, there is significant reduction in physical and neuromuscular development in neonates who exposed to higher maternal cortisol as well as P-CRH during second and third trimester respectively (80). Those neonates also express prolonged cortisol response to stress, which similar to the effect of synthetic prenatal GCs (81). Interestingly, these behavioral, cognitive and neuromuscular deficiency of offspring exposed to endogenous maternal GCs were accompanied by reduction in the volume of the areas responsible for these functions (82, 83).

Immune system disorder also noted in offspring exposed to maternal prenatal stress with higher incidence of childhood skin, respiratory and other general infections and increased antibiotics use (84). In addition, they have increased body weight which was significantly apparent at age of 10 years (85). More specifically, maternal high CRH during second trimester was found to be associated with offspring adiposity at age of 3 years (86).

2.2.1.2. Antenatal synthetic steroid (dexamethasone and betamethsone) exposure

Maternal administration of synthetic GCs such as dexamethasone and betamethasone, which are poor substrates for 11 β-HSD 2 (87), during pregnancy can cross the placenta (88) in quantities sufficient to induce immediate fetal changes such as reduction in umbilical artery pulsatility index and improved velocity (89) along with transient suppression of fetal breathing and fetal movement resulting in lowering the score of biophysical profile (90). 11 β-HSD 2 is expressed mainly in placental cytotrophoblasts, the progenitors, only upon

syncytialization into syncytiotrophoblasts (91). Li and colleagues found that up on syncytialization the expressions of SP1 transcription factor as well as the cAMP pathway are markedly activated (91).

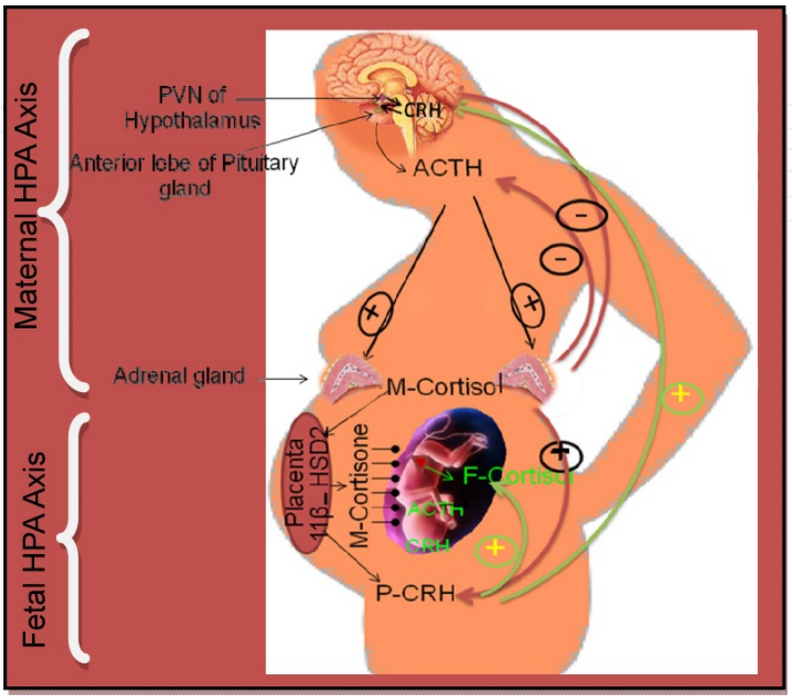

Figure 4. Fetal and maternal HPA axes are two independent systems. The P-CRH stimulates the production of both maternal and fetal cortisol. Maternal cortisol has negative feedback inhibition on her CRH and ACTH but exerts positive feedback stimulation on P-CRH. Placental 11 β-HSD 2 inactivates maternal cortisol into cortisone and hence partially protects the fetus from endogenous maternal GCs over exposure. H: Hypothalamus, P: Pituitary, HPA: Hypothalamo-Pituitary-Adrenal, P-CRH: Placental Corticotrophin Releasing Hormone, ACTH: Adreno-Corticotrophic Hormone, 11 β-HSD 2:11-β-Hydroxysteroid dehydrogenase-2, GCs:Glucocorticoids, M-Cortisol: Maternal cortisol, M-Cortisone: Maternal cortisone, PVN: Paraventricular nucleus, ⊖: Inhibition, ⊕: Stimulation.

GCs are strong inducers of HLA-G gene expression in choriocarcinoma JEG-3 cell lines. The HLA-G molecules play a pivotal role in regulating feto-maternal interface and essential for protecting the allogenic fetus from maternal immune attack (92).

After the finding that surfactant deficiency in premature infants (less than 37 weeks of gestation) is the leading cause of respiratory distress syndrome (RDS) in 1959 (93) and high mortality rate among preterm infants because of this lung immaturity (94, 95) a continuous work was done to prevent such fatal condition. Clinically, GCs has been used to prevent neonatal respiratory distress syndrome successfully (96). Thereafter, many studies found that maternal treatment of GCs will significantly decrease neonatal death due to reduction of intraventricular haemorrhage and necrotising enterocolitis beside reduction in RDS (97, 98). However, randomized controlled trials shown that no differences in the effectiveness of both dexamethasone and betamethasone in reducing the rate of respiratory distress syndrome, need for vasopressor therapy, necrotizing enterocolitis, retinopathy of

prematurity, patent ductus arteriosus, neonatal sepsis, and neonatal mortality but reduction in the frequency of intraventricular haemorrhage was more with dexamethasone compared to betamethasone (99).

When synthetic GCs administered during pregnancy they can cross placenta freely since they are not a good substrates to 11 β-HSD 2 (88) and is not bound by CBP (100). Although, the mechanism by which GCs enhance fetal lung maturity is not well established, the administration of antenatal GCs in threatened preterm labour was widely recommended by many institutes. For instance, the National Institutes of Health (NIH) published a Consensus Development Conference Statement in 1994 on the use of antenatal GCs (101) and in 2002, the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice (ACOG) supported the conclusions of the NIH consensus conference (102), whereas, the Royal College of Obstetricians and Gynecologists (RCOG) published guideline in 1996 (103) about antenatal GCs use in preterm labour which then up dated in 1999 and further in 2004.

Recently, there are many evidences that GCs induce fetal lung maturity at both transcriptional and post transcriptional levels (104-106). Pulmonary surfactant is a complex lipoprotein which main action is to reduce surface tension in the alveoli, and subsequently prevent alveolar collapse upon expiration (107). There are four major types of surfactant proteins (SP) A, B, C and D (108). GCs act mainly by increasing the surfactant protein-B (SP-B) mRNA expression at transcription level and its stability at post transcription level (109). Treatment consists of two doses of 12 mg of betamethasone given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart. Optimal benefit begins 24 hours after initiation of therapy and lasts 7 days (101). It has been recently established the use of repeated GCs courses every 14 days for those who still not delivered after the first course. Studies on animal models and also on human showed no additional benefits from repeated courses compared with single GCs course (110-112) and even can be harmful (113-116).

In fact, multiple courses of antenatal GCs have been found to be associated with reduction in ponderal measurements including birth weight, height (116-120) and birth head circumference (117, 119, 121) and higher infant blood pressure and myocardial wall thickness (122, 123) also with maternal infection such as chorioamnionitis and endometritis (116, 121, 124). Rodríguez-Pinilla also reported that antenatal exposure to single steroid course is able to produce similar effects of multiple courses on birth weight and height but not head circumference (117).

With regard to fetal bone metabolism, there were few studies addressing this subject. However, the available data do suggest that both single as well as multiple antenatal steroid courses have no detrimental effects on fetal bone metabolism as evidenced by umbilical cord serum levels of carboxy-terminal propeptide of type I procollagen, a marker for bone formation, and cross-linked carboxy-terminal telopeptide of type I procollagen, a marker of bone resorption (125-127).

The impact of maternal GCs administration antenataly on neonatal hypothalamic-pituitary-adrenal (HPA) axis has been examined extensively but data are controversy. Sandesh Kiran

and coworkers found that multiple courses of antenatal dexamethasone causing a significant decrease in RDS without adrenal suppression, decreased growth or impaired neuro-development (128). However, Schäffer and colleagues found that single course of antenatal GCs can lead to absence of stress-induced plasma cortisone and cortisol elevation in neonates at 4 days of life (129). On the other hand, Davis reported that antenatal GCs administration in threatened preterm labour was associated with higher pain-induced plasma cortisol elevation despite no difference in baseline levels than non-treated matched infants at 24 hr after birth (81). Others have assessed the impact of antenatal corticosteroid courses on HPA axis by measuring neonatal 17-OHP in filter-paper blood spots collected between 72 and 96 hr after birth, which usually used for screening the neonates for CAH (Section 1.2.1) (130). These studies revealed a significant reduction of blood 17-OHP in those received multiple courses compared to non-treated matched neonates (130). This fact raise the suspicion in the effectiveness of this screening test in this particular group of neonates as prenatal steroid-induced reduction in 17-OHP could be interpreted falsely as negative test in affected newborns. Ng et al found that at postnatal day 7 and 14 neonatal plasma ACTH and cortisone levels measured after human corticotrophin releasing hormone (hCRH) stimulation test was mildly lower in those exposed to multiple dexamethasone injections antenataly than none treated neonates. Interestingly, there was a negative correlation between plasma cortisone and the number of dexamethasone injections antenataly (131). These finding strongly indicate that antenatal steroid therapy, multiple courses in particular, has impact, which could be transient, on HPA axis harmony and neonatal observation during the first few days is warranted. Animal model of prenatal betamethasone using guinea pigs reported same finding that ACTH and plasma cortisol both suppressed by prenatal betamethasone treatment. This was assosiated with significant reduction in hippocampal mineralococrticoids receptor mRNA and protein expression especially in male offspring with no much difference among GR mRNA and protein expression (132).

It has been found that multiple prenatal steroid courses are not associated with a deleterious effect on auditory neural maturation when assessed at 24 hr after birth (133). However, the use of multiple dexamethasone but not betamethasone are associated with persistent increases in brain parenchymal echogenicity in preterm infants (134) as well as cystic leukomalacia and neurodevelopmental delay at 2 years of age (135). Animal models of prenatal steroid therapy presented some evidence regarding possible mechanism by which antenatal glucocorticoids prevent intraventricular haemorrhage in preterm infants. In mice, prenatal steroid therapy can induce choroid plexus capillary stability and maturation by increasing basement membrane thickness and integrity with subsequent reduction in both peri and intraventricular haemorrhage (136). The frequency and severity of periventricular and intraventricular haemorrhage were even less if vitamin K injection administered antenataly along with steroid course (137).

More recent data comparing the efficacy of single steroid course with multiple courses stated that there were no significant differences in the frequency of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis and neonatal mortality in neonates receiving either single betamethasone course or multiple courses (138).

According to the same study, the use of multiple courses is not superior to single course. Similar beneficial effect was noted from the use of single and multiple antenatal steroid courses in decreasing the need for postnatal blood pressure support in extreme preterm infants born between 24 to 28 weeks of age (139).

On the same bases, the ACOG Committee on Obstetric Practice (2011) has published its opinion regarding the use of multiple courses. The committee recommended the use of single corticosteroids course to all pregnant women at risk of preterm delivery at 24 to 34 weeks gestation. Another single rescue course of antenatal corticosteroids may be considered if the initial steroid course was given more than 2 weeks earlier (140).

2.2.2. Long term effects of prenatal GCs overexposure

There are accumulating evidence about solid role played by fetal overexposure to both endogenous or synthetic GCs and the risk of developing metabolic and cardiovascular disease in adulthood (141, 142). This remote response to an intrauterine insult has been termed (fetal programming of adult disease).

3. Fetal programming of adult disease

Programming refers to physiological, metabolic, or behavioral adaptation resulting from exposure to or lack of hormones, nutrients, stress, and other agents at critical period during embryonic and fetal development. These insults may encode the function of organs and systems and manifested later as elevated risk for disease in adult life (143, 144). The concept of programming was emerged from many epidemiological studies. For instant, follow up study of a cohort of men who were born during Duch famine in 1944-45 found that exposure to undernutrition during the first half of pregnancy were significantly associated with obesity at adulthood (145). subsequent studies have linked the low birth weight with developing of hypertension, ischaemic heart disease, glucose intolerance, insulin resistance, type 2 diabetes, hyperlipidaemia, hypercortisolaemia, obesity, obstructive pulmonary disease, renal failure and reproductive disorders in the adult (146).

The factors that can programme disease risk in later life are multiple but interact together and include undernutrition (147), stress(148) and endocrine disturbances (149). It has been found that maternal undernutrition leads to decreased placental and fetal birth weight associated with elevated maternal plasma GCs and reduced placental expression of 11 β-Hydroxysteroid Dehydrogenase-2 and subsequently fetal over exposure to maternal corticosterone in rat (150). Maternal low protein diet, for instance, programmed the development of hypertension (151, 152), glucose intolerance (153, 154) and even feeding behavioral abnormalities (155). In human, fetal over exposure to endogenous maternal GCs, such as in maternal psychological stress, programmed the development of metabolic syndrome with higher BMI and body fat percentage, insulin resistance, and atherogenic lipid profile in the offspring at adult life (156). Moreover, adult offspring exposed to prenatal maternal stress, and hence high endogenous GCs, have altered T-helper 1 and 2 balance and abnormal cytokines and ultimately become more prone to develop autoimmune

disorders and asthma (157). Similarly, there was impaired cognitive performance as well as memory in the offspring who exposed to maternal stress and higher endogenous GCs. This disturbances in mental function was associated with altered HPA axis in later life where ACTH was increased and plasma cortisol level was decreased (158).

Interestingly, the same programming effect was observed using synthetic GCs such as dexamethasone, which is poor substrate to 11 β-Hydroxysteroid Dehydrogenase-2 (142, 159). Prenatal exposure to synthetic GCs resulted in anxiety and depressive-like behavior in adult offspring. There was altered brain structure with significant increase in volume of the bed nucleus of the stria terminalis and on the other hand decrease amygdala volume due to dendritic atrophy. Dopamin was reduced and dopamin receptor 2 was up regulated in this area (160, 161).

Dexamethasone exposure during late gestation is also able to alter the hepatic and adipose tissue activity and mRNA expression of β-HSD 1 in marmoset monkey with subsequent development of obesity and overt metabolic syndrome (162). It is clear from these data that both fetal exposure to undernutrition, as stress event that lead to fetal over exposure to endogenous maternal GCs, as well as overexposure to synthetic GCs, which are poor substrates to placental 11 β-HSD 2, share common mechanistic pathway in the programming of metabolic syndrome in the offspring at adult life.

3.1. Proposed mechanism of fetal programming of adult disease

The concept of the programming has its roots since 50 years ago (163) and proven by both animal (152, 164) and human studies (119, 149), however, the mechanism that events during intrauterine life are carried in the memory of every molecule, gene, cell, tissue and systems` organs of the body still not completely revealed. Many hypotheses have been proposed with their inherited power and weakness. These include epigenetic modifications of DNA, altered gene expression and regulation, disruption of organ structure by variation in cell number and differentiation and apoptotic remodeling (165, 166). "Hormonal imprinting" where exposure to abnormal levels of a particular hormone during specific window of tissue plasticity is able to exert lifelong abnormal metabolism is another proposed mechanism (167).

3.1.1. Tissue remodeling

In maternal undernutrition model, programming was found to be associated with decreased organ size and total cell mass. Programming of diabetes, in this model, was accompanied by altered pancreatic structure, with predominantly a decrease in β-cell mass (153) due, primarily, to decreased proliferation and increased apoptosis (168). In this model, last week of rat pregnancy was identified as the critical window of programming. Similarly, programming of hypertension was linked to decreased number of nephrons and impaired renal electrolytes and fluid balance (169). GCs, both synthetic one and endogenous, are mediating their programming effects through similar mechanism. As mentioned previously that the observed psychological, behavioral and neuromuscular disturbances were all

associated with decreased volume of brain area responsible on that particular function. Moreover, dexamethasone prenatally caused marked reduction in thymus (170). Therefore, antenatal exposure to glucocorticoids above the physiological limit will perturb the growth and ultimate size of the developing fetal organs and eventually their functional capacity which then manifested as disease in adult life.

3.1.2. Epigenetic DNA modification

Epigenetic phenomenon refers to altered heritable genomic function without change in DNA sequence (171). Epigenetic modification involves mainly DNA methylation, histone modification, and miRNA effects (172). DNA methylation has been well explored. In this case there is methylation of cytosine residues within CpG dinucleotides. When this abnormal methylation of CpG islands occur in the promoter region of genes it will result in silencing of genetic information and subsequently to altered biological function (171). Methylation status is a dynamic status and changes are observed since fertilization where both maternal and paternal genomes undergo extensive demethylation followed by selective methylation just prior to implantation (173). This alteration in methylation status has been suggested to play role in cell differentiation and organ development (174). DNA methylation blocks the binding of transcription factors to the promoter of the target gene (Figure 5) and hence prevent gene expression or it promote the binding of the methyl CpG binding protein (MeCP2) which recruits other protein complexes to bind to DNA resulting in a closed chromatin structure and transcriptional silencing (174).

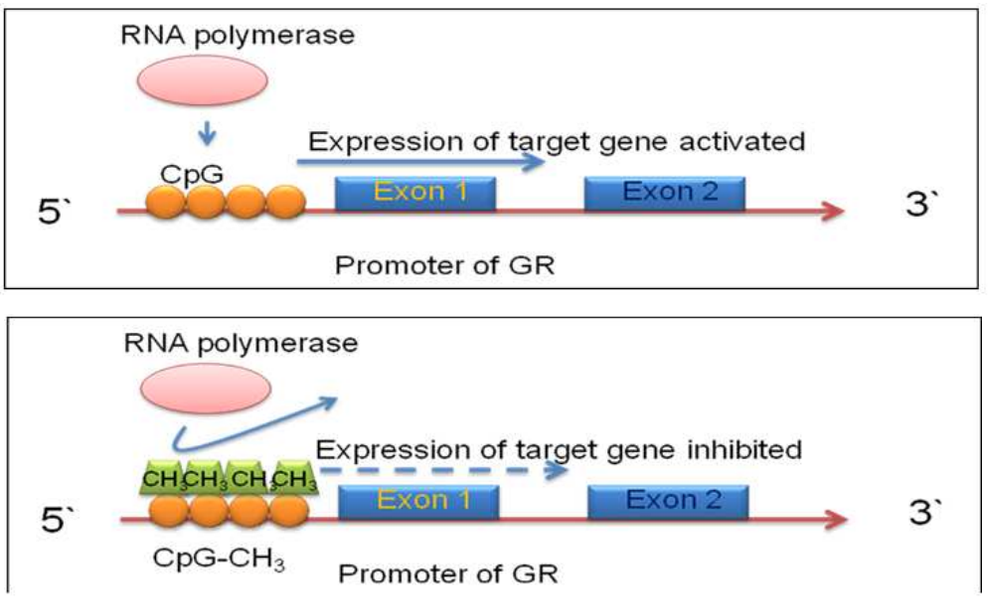

Figure 5. Epigenetic modification of GR promoter by CpG altered methylation.

Maternal low protein diet during pregnancy as experimental model of programming of metabolic syndrome like phenotype has been found to be associated with altered DNA methylation in key genes. For instance, maternal low protein diet resulted in GR over expression and 11 β-HSD 2 decreased expressions in liver, lung, kidney and brain of the

offspring (175). GCs induce the hepatic expression and activity of phosphoenolpyruvate carboxykinase (PEPCK) the key enzyme responsible for gluconeogenesis and subsequently produce insulin resistance in this model (176). Interestingly, these changes in expression of target genes were associated with altered methylation status in their promoter area. Namely, GR promoter was found to be hypomethylated in liver tissue of 5 weeks old offspring (177). Some preliminary evidence suggest that hypomethylation of GR occur during early embryogenesis even before cell line differentiation, this was because of finding that GR hypomethylation found in all examined tissue of the offspring in this model (174). GR promoter hypomethylation was associated with histone modification, due to decreased acetylation, in way facilitating transcription (178). Supplementation of maternal low protein diet with glycine or folic acid prevented the development of metabolic syndrome like phenotype as well as GR promoter hypomethylation. Similarly, perinatal stress exposure resulted in altered stress response in the offspring which found to be accompanied with GR promoter hypermethylation at specific CpG dinucleotides in the hippocampus of the offspring. These changes were reversed in adult brain with intra-cranial histone deacetylase inhibitor administration (179). Similarly, in human fetal exposure to maternal stress during second and third trimesters was associated with increased methylation in specific CpG sequence in axon 1F of the GR gene analyzed in cord blood mononuclear cells and at 3 months of offspring age there was significant association between higher CpG methylation in GR gene and higher plasma cortisol response to stress (180). These epigenetic DNA modification seen in antenatal malnutrition or dexamethasone exposure are transmitted to the second generation (181), however, in human it needs to be further explored. It has been suggested that GCs exposure, either endogenous as in maternal psychological stress or in food deprivation or due to antenatal synthetic GCs administration, lead to altered DNA methylation via reduce folic acid availability (182). N5- methyltetrahydrofolate is folic acid derivative and it is considered one of the important methyl donors, therefore, any constrain on folic acid availability will affect methyl donors availability as well.

All these valuable data gave strong evidence that intrauterine life environment has crucial role in human health during adulthood and that the unfavorable conditions will act on the basic unit in the body, that is DNA. Therefore, altered DNA function via epigenetic modification will constrain the functional capacity of key organs when needed to work with their full capacity at adult life and ultimately expressed as disease. The understanding of the mechanism of disease can open the door for discovering early markers for the risk of developing disease and importantly more targeted therapeutic strategies.

3.1.3. Glucocorticoids over exposure

Most of animal models of disease programming and human studies including epidemiological data indicated that glucocorticoids have crucial role in the development of cardio-metabolic and neouro-psychological disease at adulthood. This deleterious effect of glucocorticoids can be exerted directly up on maternal administration of synthetic glucocorticoids and by stress induced endogenous maternal glucocorticoids hypersecretion or indirectly through other types of stress such as food restriction. The development of low

birth weight, hypertension, glucose intolerance and insulin resistance in offspring of rat dams fed low protein diet during pregnancy were linked to decreased placental 11 β-HSD 2 expression and activity which resulted in high influx of maternal glucocorticoids to fetal compartment in addition to increased sensitivity of key metabolic organs such as liver, kidney and adipose tissue to glucocorticoids secondary to increased GR expression in these organs (175, 183). The development of metabolic syndrome like phenotype in this animal model has been replicated in human offspring who were exposed to prenatal synthetic glucocorticoids due to threatened preterm delivery to induce lung maturity and also in human offspring who were exposed to high maternal glucocorticoids secondary to maternal stress during pregnancy. Therefore, fetal glucocorticoids over exposure is the main programming pathway despite the variation in the prenatal insult. This hypothesis has many supporting evidence from low protein diet model and other human studies. In rodent, treatment of pregnant dams with placental 11 β-HSD 2 inhibitor, carbenoxolone, resulted in low birth weight and hypertension at adulthood (141). Hypertension in low protein model also was glucocorticoid dependent as maternal adrenalectomy significantly reduced the blood pressure to control levels and corticosterone replacement restored the hypertensive state seen these exposed offspring (151). In human, the placental 11 β-HSD 2 activity correlated with birth weight (184) and reduced in pre-eclampsia (185) and in intrauterine growth restricted fetuses (186). Moreover, 11 β-HSD 2 gene mutation constantly resulted in lower fetal birth weight compared to normal human fetus (187). High maternal GCs associated with decreased placental 11 β-HSD 2, elevated fetal plasma GCs, lower hepatic 11 β-HSD 2 protein expression and enzyme activity which cause over expression and activity of key hepatic gluconeogenesis enzyme, phosphoenolpyruvate kinase (PEPCK), which is linked to insulin resistance and glucose intolerance. In the kidney, the main role of 11 β-HSD 2 is to prevent GCs occupying and activating mineralocorticoid receptor (MR) (188), see figure 6.

GCs-exposed offspring has decreased 11 β-HSD 2 expression and increased GR expression as well as GR promoter hypomethylation in kidney (189). Cortisol will then exert mineralocorticoid activity through MR binding in kidney and resulted in sodium and water retention, hypokalaemia, low plasma renin and aldosterone concentrations, and eventually hypertension in adult life (190). In brain the observed cognitive deficit, altered memory and psychological disturbances in GCs exposed offspring was associated with decreased GR expression in hippocampus (191), which could block the negative feedback regulation of HPA axis by plasma cortisol and hence resulted in abnormal regulation of this crucial nuerohormonal axis. GCs induce the expression of key lipogenic transcription factor, Sterol regulatory element binding protein-1c (SREBP-1c) in liver (192). SREBP-1c transgenic mice, with mRNA and protein over expression of this nuclear factor, developed hyperinsulinaemia, hyperglycaemia, and hepatic steatosis (193, 194).

Interestingly, the metabolic syndrome like phenotype seen in low-protein diet exposed offspring was associated with abnormal expression of SREBP-1c. SREBP-1c mRNA and protein expression were both suppressed from birth until age 9 months in the rat offspring. At 18 months, however, marked over expression seen specially in hepatic tissue with

development of non-alcoholic fatty liver, hypercholestreamia, hpertriglycerideamia, hyperglycemia and insulin resistance (147).

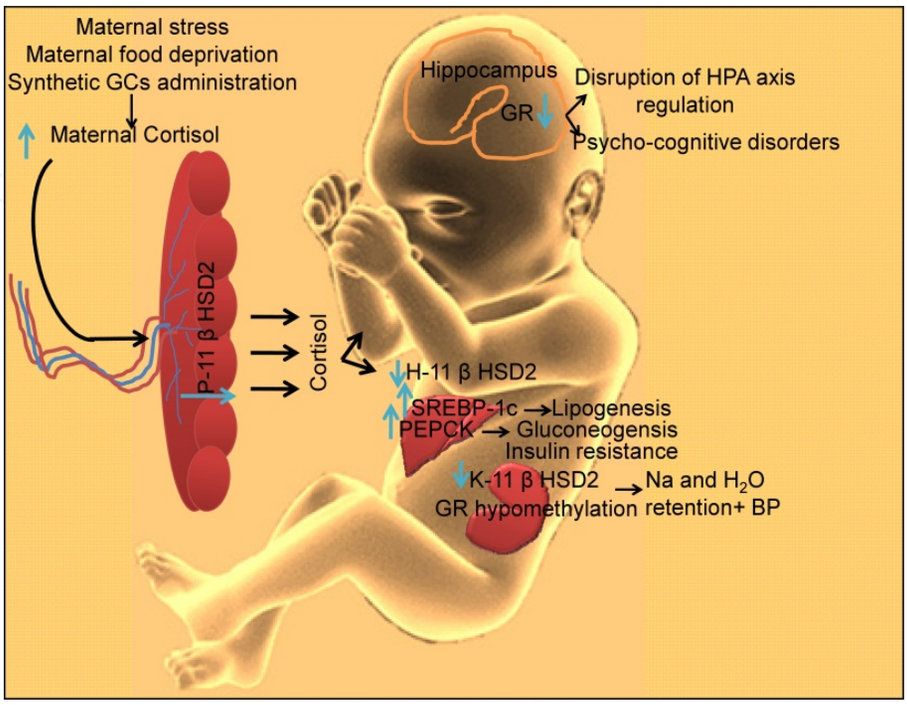

Figure 6. Glucocorticoids central role in the programming of the adult disease. Prenatal exposure to high maternal or synthetic glucocorticoids associated with decreased P-11βHSD2, K-11βHSD2 and H-11βHSD2 expression and activity. In liver this will induce SREBP-1c and lipogenesis and PEPCK and hepatic gluconeogenesis. In kidney, GR hypomethylation and decreased K-11βHSD2 activity associated with more Na and H_2O retention and eventually high BP. P-11βHSD2: Placental 11β Hydroxysteroid dehydrogenase 2, K: Kidney, H: Hepatic, SREBP-1c: Sterol Regulatory Element Binding Protein-1c, PEPK: Phosphoenolpyruvate kinase, Na: Sodium, BP: Blood pressure.

4. Conclusions

The understanding of pathogenesis of adult cardio-metabolic and psycho-cognitive disorders is now advanced beyond the idea that such diseases are result of current behavioral and environmental factors. It is well established that adult health originated from wellbeing during fetal life or even at gametes stage. Grandparents' environmental challenges can have impact on human health many generations later. In fact, factors which operate at early life will increase the individual`s susceptibility and vulnerability to adverse environmental events in later life. It is obvious now that different early life environmental events share common programming pathway. The mechanism of programming started to be revealed which include epigenetic DNA modification and promoter methylation status resulting in altered gene expression as well as glucocorticoids over exposure as a primary mechanism where as tissue remodeling and decreased organ and body size as a secondary mechanism. Glucocrticoids over exposure is the main triggering stimulus in this programming, therefore the widely clinical use of prenatal glucocorticoids such as betamethasone and dexamethasone to induce lung maturity in preterm fetus need to be

carefully evaluated since they access fetal compartment very easily. Introduction of multiple courses of glucocorticoids as a routine should be discouraged and instead it should be restricted to wisely selected cases. The maximum number of safest courses and lowest therapeutic dose of each subsequent course should be standardized. However, prenatal glucocorticoids have provided the suitable model to study the effects of direct maternal administration of this programming hormone in human candidates. Notwithstanding, these studies still in their neonatal stage and extensive research in this particular area is warranted. The identification of how early life unfavorable environment still able to express pathogenesis at adulthood is crucial to set up pre-disease markers which can be applied clinically in health screening even before the disease itself develops. This will lead to early behavioral and life style interventions which may postponed the onset of disease for many years or even freeze the pathogenesis at its pre-disease stage. Obviously this will lead to decrease financial burden on the health authorities and will markedly cuts the expenses of medical and surgical treatment of the resulted complications.

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5. References

[1] Addison T. Anemia-disease of supra renal capsule. Med Gazette 1849;43:517-518.
[2] Addison T. On the constitutional and local Effects of Disease of the Supra-Renal Capsules. Samuel Highley, London 1855.
[3] Graner JL. Addison, pernicious anemia and adrenal insufficiency. CMAJ. 1985;133(9):855-7.
[4] Lloyd M. Philip Showalter Hench, 1896-1965. Rheumatology (Oxford) 2002;41(5):582-4.
[5] Nørgaard P, Poulsen H. Glucocorticoid receptors in human malignancies: a review. Ann Oncol. 1991;2(8):541-57.
[6] Chrousos GP, Kino T. Glucocorticoid signaling in the cell. Expanding clinical implications to complex human behavioral and somatic disorders. Ann N Y Acad Sci 2009;1179:153-66.
[7] Zanchi NE, Filho MrAdS, Felitti V, Nicastro H, Lorenzeti FbM, Lancha AH. Glucocorticoids: Extensive physiological actions modulated through multiple mechanisms of gene regulation. Journal of Cellular Physiology 2010;224(2):311-315.

[8] Dallman MF, Strack AM, Akana SF, Bradbury MJ, Hanson ES, Scribner KA, et al. Feast and Famine: Critical Role of Glucocorticoids with Insulin in Daily Energy Flow. Frontiers in Neuroendocrinology 1993;14(4):303-347.
[9] Gaillard R. Interaction between the hypothalamo-pituitary-adrenal axis and the immunological system. Ann Endocrinol (Paris). 2001;62(2):155-63.
[10] Da Silva JA. Sex hormones and glucocorticoids: interactions with the immune system. Ann N Y Acad Sci 1999;876:102-17; discussion 117-8.
[11] Giannopoulos G. Early events in the action of glucocorticoids in developing tissues. J Steroid Biochem 1975;6(5):623-31.
[12] Iavazzo C, Myriokefalitaki E, Ntziora F, Bozemberg T, Baskozos I, Papargyriou T, et al. Classic congenital adrenal hyperplasia with virilisation and salt-wasting: from birth to the adult life. Bratisl Lek Listy 2011;112(11):651-2.
[13] Speiser PW, Laforgia N, Kato K, Pareira J, Khan R, Yang SY, et al. First trimester prenatal treatment and molecular genetic diagnosis of congenital adrenal hyperplasia (21-hydroxylase deficiency). J Clin Endocrinol Metab 1990;70(4):838-48.
[14] Forest MG, David M. Antenatal diagnosis and treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Rev Prat 1991;41(13):1183-7.
[15] Dorr H, Sippell W, Haack D, Bidlingmaier F, Knorr D. Pitfalls of Prenatal treatment of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. Program and Abstract. In: 25th Annual meeting of the European Society for Paediatric Endocrinology; 1986; Zurich; 1986.
[16] Evans MI, Chrousos GP, Mann DW, Larsen JW, Jr., Green I, McCluskey J, et al. Pharmacologic suppression of the fetal adrenal gland in utero. Attempted prevention of abnormal external genital masculinization in suspected congenital adrenal hyperplasia. Jama 1985;253(7):1015-20.
[17] Mercado AB, Wilson RC, Cheng KC, Wei JQ, New MI. Prenatal treatment and diagnosis of congenital adrenal hyperplasia owing to steroid 21-hydroxylase deficiency. Journal of Clinical Endocrinology & Metabolism 1995;80(7):2014-20.
[18] Charmandari E, Brook CG, Hindmarsh PC. Why is management of patients with classical congenital adrenal hyperplasia more difficult at puberty? Arch Dis Child 2002;86(4):266-9.
[19] Kino T, Chrousos G. Glucocorticoid effects on gene expression. In: Steckler T KN, Reul JMHM, editor. Handbook of Stress and the Brain. Amsterdam: Elsevier; 2005. p. 295-311.
[20] Chrousos GP. The glucocorticoid receptor gene, longevity, and the complex disorders of Western societies. Am J Med 2004;117(3):204-7.
[21] Chrousos GP, Charmandari E, Kino T. Glucocorticoid action networks--an introduction to systems biology. J Clin Endocrinol Metab 2004;89(2):563-4.
[22] Galon J, Franchimont D, Hiroi N, Frey G, Boettner A, Ehrhart-Bornstein M, et al. Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. Faseb J 2002;16(1):61-71.
[23] Cameron A, Henley D, Carrell R, Zhou A, Clarke A, Lightman S. Temperature-responsive release of cortisol from its binding globulin: a protein thermocouple. J Clin Endocrinol Metab 2010;95(10):4689-95.

[24] David EG, Armen H, Tashjian J, Ehrin JA, April WA. Pharmacology of the Adrenal Cortex. In: David EG, editor. Principles of pharmacology: the pathophysiologic basis of drug therapy. second ed. USA: Lippincott Williams & Wilkins; 2008. p. 493-508.
[25] Nicolaides NC, Galata Z, Kino T, Chrousos GP, Charmandari E. The human glucocorticoid receptor: molecular basis of biologic function. Steroids 2010;75(1):1-12.
[26] Hollenberg SM, Weinberger C, Ong ES, Cerelli G, Oro A, Lebo R, et al. Primary structure and expression of a functional human glucocorticoid receptor cDNA. Nature 1985;318(6047):635-41.
[27] Duma D, Jewell CM, Cidlowski JA. Multiple glucocorticoid receptor isoforms and mechanisms of post-translational modification. J Steroid Biochem Mol Biol 2006;102(1-5):11-21.
[28] Bamberger CM, Bamberger AM, de Castro M, Chrousos GP. Glucocorticoid receptor beta, a potential endogenous inhibitor of glucocorticoid action in humans. J Clin Invest 1995;95(6):2435-41.
[29] Chung CC, Shimmin L, Natarajan S, Hanis CL, Boerwinkle E, Hixson JE. Glucocorticoid receptor gene variant in the 3' untranslated region is associated with multiple measures of blood pressure. J Clin Endocrinol Metab 2009;94(1):268-76.
[30] Hench P. Effects of cortisone in the rheumatic diseases. Lancet 1950;2(6634):483-4.
[31] Cupps TR, Edgar LC, Thomas CA, Fauci AS. Multiple mechanisms of B cell immunoregulation in man after administration of in vivo corticosteroids. J Immunol 1984;132(1):170-5.
[32] Sbiera S, Dexneit T, Reichardt SD, Michel KD, van den Brandt J, Schmull S, et al. Influence of short-term glucocorticoid therapy on regulatory T cells in vivo. PLoS One 2011;6(9):e24345.
[33] Cox G. Glucocorticoid treatment inhibits apoptosis in human neutrophils. Separation of survival and activation outcomes. J Immunol 1995;154(9):4719-25.
[34] Nakagawa M, Bondy GP, Waisman D, Minshall D, Hogg JC, van Eeden SF. The effect of glucocorticoids on the expression of L-selectin on polymorphonuclear leukocyte. Blood 1999;93(8):2730-7.
[35] van der Goes A, Hoekstra K, van den Berg TK, Dijkstra CD. Dexamethasone promotes phagocytosis and bacterial killing by human monocytes/macrophages in vitro. J Leukoc Biol 2000;67(6):801-7.
[36] Curtiss PH, Jr., Clark WS, Herndon CH. Vertebral fractures resulting from prolonged cortisone and corticotropin therapy. J Am Med Assoc 1954;156(5):467-9.
[37] Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. Ann Intern Med 1990;112(5):352-64.
[38] Adler RA, Rosen CJ. Glucocorticoids and osteoporosis. Endocrinol Metab Clin North Am 1994;23(3):641-54.
[39] Canalis E. Clinical review 83: Mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis. J Clin Endocrinol Metab 1996;81(10):3441-7.
[40] Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endocrinol Metab Clin North Am 1998;27(2):465-83.
[41] Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. J Bone Miner Res 1999;14(7):1061-6.

[42] Pocock NA, Eisman JA, Dunstan CR, Evans RA, Thomas DH, Huq NL. Recovery from steroid-induced osteoporosis. Ann Intern Med 1987;107(3):319-23.
[43] Reid IR, Heap SW. Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy. Arch Intern Med 1990;150(12):2545-8.
[44] Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res 2000;15(6):1006-13.
[45] Vermaat H, Kirtschig G. Prevention and treatment of glucocorticoid-induced osteoporosis in daily dermatologic practice. Int J Dermatol 2008;47(7):737-42.
[46] Sun L, Trausch-Azar JS, Muglia LJ, Schwartz AL. Glucocorticoids differentially regulate degradation of MyoD and Id1 by N-terminal ubiquitination to promote muscle protein catabolism. Proc Natl Acad Sci U S A 2008;105(9):3339-44.
[47] Nishimura T, Matsumoto T, Nishino M, Tomita K. Histopathologic study of veins in steroid treated rabbits. Clin Orthop Relat Res 1997(334):37-42.
[48] Weinstein RS, Nicholas RW, Manolagas SC. Apoptosis of osteocytes in glucocorticoid-induced osteonecrosis of the hip. J Clin Endocrinol Metab 2000;85(8):2907-12.
[49] Souverein PC, Berard A, Van Staa TP, Cooper C, Egberts AC, Leufkens HG, et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. Heart 2004;90(8):859-65.
[50] Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;141(10):764-70.
[51] White KP, Driscoll MS, Rothe MJ, Grant-Kels JM. Severe adverse cardiovascular effects of pulse steroid therapy: is continuous cardiac monitoring necessary? J Am Acad Dermatol 1994;30(5 Pt 1):768-73.
[52] Berg AL, Nilsson-Ehle P. ACTH lowers serum lipids in steroid-treated hyperlipemic patients with kidney disease. Kidney Int 1996;50(2):538-42.
[53] Choi HK, Seeger JD. Glucocorticoid use and serum lipid levels in US adults: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2005;53(4):528-35.
[54] Miller SE, Neilson JM. Clinical Features of the Diabetic Syndrome Appearing after Steroid Therapy. Postgrad Med J 1964;40:660-9.
[55] Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J. Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med 1994;154(1):97-101.
[56] Olefsky JM, Kimmerling G. Effects of glucocorticoids on carbohydrate metabolism. Am J Med Sci 1976;271(2):202-10.
[57] Minden SL, Orav J, Schildkraut JJ. Hypomanic reactions to ACTH and prednisone treatment for multiple sclerosis. Neurology 1988;38(10):1631-4.
[58] Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. Psychoneuroendocrinology 1996;21(1):25-31.
[59] Keenan PA, Jacobson MW, Soleymani RM, Mayes MD, Stress ME, Yaldoo DT. The effect on memory of chronic prednisone treatment in patients with systemic disease. Neurology 1996;47(6):1396-402.

[60] Souza-Talarico JNd, Marin M-F, Sindi S, Lupien SJ. Effects of stress hormones on the brain and cognition Evidence from normal to pathological aging. Dement Neuropsychol 2011;5(1):8-16.
[61] Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 1991;115(10):787-96.
[62] Chrousos GA, Kattah JC, Beck RW, Cleary PA. Side effects of glucocorticoid treatment. Experience of the Optic Neuritis Treatment Trial. Jama 1993;269(16):2110-2.
[63] Derk CT, DeHoratius RJ. Systemic lupus erythematosus and acute pancreatitis: a case series. Clin Rheumatol 2004;23(2):147-51.
[64] Mastorakos G, Ilias I. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. Ann N Y Acad Sci 2003;997:136-49.
[65] Seckl JR. Glucocorticoid programming of the fetus; adult phenotypes and molecular mechanisms. Mol Cell Endocrinol 2001;185(1-2):61-71.
[66] Fowden AL, Forhead AJ. Endocrine mechanisms of intrauterine programming. Reproduction 2004;127(5):515-26.
[67] Dy J, Guan H, Sampath-Kumar R, Richardson BS, Yang K. Placental 11beta-hydroxysteroid dehydrogenase type 2 is reduced in pregnancies complicated with idiopathic intrauterine growth Restriction: evidence that this is associated with an attenuated ratio of cortisone to cortisol in the umbilical artery. Placenta 2008;29(2):193-200.
[68] Huh SY, Andrew R, Rich-Edwards JW, Kleinman KP, Seckl JR, Gillman MW. Association between umbilical cord glucocorticoids and blood pressure at age 3 years. BMC Med 2008;6:25.
[69] Sanchez MM, Young LJ, Plotsky PM, Insel TR. Distribution of corticosteroid receptors in the rhesus brain: relative absence of glucocorticoid receptors in the hippocampal formation. J Neurosci 2000;20(12):4657-68.
[70] Raschke C, Schmidt S, Schwab M, Jirikowski G. Effects of betamethasone treatment on central myelination in fetal sheep: an electron microscopical study. Anat Histol Embryol 2008;37(2):95-100.
[71] Kostovic I, Judas M, Rados M, Hrabac P. Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. Cereb Cortex 2002;12(5):536-44.
[72] Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997;387(2):167-78.
[73] Levitt P. Structural and functional maturation of the developing primate brain. J Pediatr 2003;143(4 Suppl):S35-45.
[74] Seckl JR, Meaney MJ. Glucocorticoid "programming" and PTSD risk. Ann N Y Acad Sci 2006;1071:351-78.
[75] Murphy VE, Clifton VL. Alterations in human placental 11beta-hydroxysteroid dehydrogenase type 1 and 2 with gestational age and labour. Placenta 2003;24(7):739-44.
[76] Lowry PJ. Corticotropin-releasing factor and its binding protein in human plasma. Ciba Found Symp 1993;172:108-15; discussion 115-28.

[77] Cheng YH, Nicholson RC, King B, Chan EC, Fitter JT, Smith R. Corticotropin-releasing hormone gene expression in primary placental cells is modulated by cyclic adenosine 3',5'-monophosphate. J Clin Endocrinol Metab 2000;85(3):1239-44.
[78] Sandman CA, Davis EP, Buss C, Glynn LM. Prenatal programming of human neurological function. Int J Pept 2011;2011:837596.
[79] Sandman CA, Wadhwa PD, Chicz-DeMet A, Porto M, Garite TJ. Maternal corticotropin-releasing hormone and habituation in the human fetus. Dev Psychobiol 1999;34(3):163-73.
[80] Ellman LM, Schetter CD, Hobel CJ, Chicz-Demet A, Glynn LM, Sandman CA. Timing of fetal exposure to stress hormones: effects on newborn physical and neuromuscular maturation. Dev Psychobiol 2008;50(3):232-41.
[81] Davis EP, Waffarn F, Sandman CA. Prenatal treatment with glucocorticoids sensitizes the hpa axis response to stress among full-term infants. Developmental Psychobiology 2011;53(2):175-183.
[82] Buss C, Davis EP, Muftuler LT, Head K, Sandman CA. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9-year-old children. Psychoneuroendocrinology 2010;35(1):141-53.
[83] Connolly JD, Goodale MA, Menon RS, Munoz DP. Human fMRI evidence for the neural correlates of preparatory set. Nat Neurosci 2002;5(12):1345-52.
[84] Beijers R, Jansen J, Riksen-Walraven M, de Weerth C. Maternal prenatal anxiety and stress predict infant illnesses and health complaints. Pediatrics 2010;126(2):e401-9.
[85] Li J, Olsen J, Vestergaard M, Obel C, Baker JL, Sorensen TI. Prenatal stress exposure related to maternal bereavement and risk of childhood overweight. PLoS One 2010;5(7):e11896.
[86] Gillman MW, Rich-Edwards JW, Huh S, Majzoub JA, Oken E, Taveras EM, et al. Maternal corticotropin-releasing hormone levels during pregnancy and offspring adiposity. Obesity (Silver Spring) 2006;14(9):1647-53.
[87] Diederich S, Eigendorff E, Burkhardt P, Quinkler M, Bumke-Vogt C, Rochel M, et al. 11beta-hydroxysteroid dehydrogenase types 1 and 2: an important pharmacokinetic determinant for the activity of synthetic mineralo- and glucocorticoids. J Clin Endocrinol Metab 2002;87(12):5695-701.
[88] Anderson AB, Gennser G, Jeremy JY, Ohrlander S, Sayers L, Turnbull AC. Placental transfer and metabolism of betamethasone in human pregnancy. Obstet Gynecol 1977;49(4):471-4.
[89] Thuring A, Malcus P, Marsal K. Effect of maternal betamethasone on fetal and uteroplacental blood flow velocity waveforms. Ultrasound Obstet Gynecol 2011;37(6):668-72.
[90] Rotmensch S, Liberati M, Celentano C, Efrat Z, Bar-Hava I, Kovo M, et al. The effect of betamethasone on fetal biophysical activities and Doppler velocimetry of umbilical and middle cerebral arteries. Acta Obstet Gynecol Scand 1999;78(9):768-73.
[91] Li JN, Ge YC, Yang Z, Guo CM, Duan T, Myatt L, et al. The Sp1 Transcription Factor Is Crucial for the Expression of 11Î²-Hydroxysteroid Dehydrogenase Type 2 in Human Placental Trophoblasts. Journal of Clinical Endocrinology & Metabolism 2011;96(6):E899-E907.

[92] Akhter A, Das V, Naik S, Faridi RM, Pandey A, Agrawal S. Upregulation of HLA-G in JEG-3 cells by dexamethasone and hydrocortisone. Arch Gynecol Obstet 2012;285(1):7-14.
[93] Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. AMA J Dis Child 1959;97(5, Part 1):517-23.
[94] Dollfus C, Patetta M, Siegel E, Cross AW. Infant mortality: a practical approach to the analysis of the leading causes of death and risk factors. Pediatrics 1990;86(2):176-83.
[95] Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. Pediatrics 2004;114(2):372-6.
[96] Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50(4):515-25.
[97] Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;3:CD004454.
[98] Elimian A, Verma U, Canterino J, Shah J, Visintainer P, Tejani N. Effectiveness of antenatal steroids in obstetric subgroups. Obstet Gynecol 1999;93(2):174-9.
[99] Elimian A, Garry D, Figueroa R, Spitzer A, Wiencek V, Quirk JG. Antenatal betamethasone compared with dexamethasone (betacode trial): a randomized controlled trial. Obstet Gynecol 2007;110(1):26-30.
[100] Hughes I, Cutfield W. The adrenal cortex. In: Gluckman P, Heymann M, editors. Pediatrics, perinatology, the scientific basis. London: Arnold; 1996. p. 500- 514.
[101] NIH. ACOG committee opinion. Antenatal corticosteroid therapy for fetal maturation. Number 147--December 1994. Committee on Obstetric Practice. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 1995;48(3):340-2.
[102] ACOG. ACOG committee opinion. Antenatal corticosteroid therapy for fetal maturation. American College of Obstetricians and Gynecologists; 2002 Jul.
[103] RCOG. RCOG Guidelines Number 7 ACS to prevent respiratory distress syndrome. London: RCOG; 1996.
[104] Tillis CC, Huang HW, Bi W, Pan S, Bruce SR, Alcorn JL. Glucocorticoid regulation of human pulmonary surfactant protein-B (SP-B) mRNA stability is independent of activated glucocorticocorticoid receptor. American Journal of Physiology - Lung Cellular and Molecular Physiology 2011;300(6):L940-L950.
[105] Whitsett JA, Matsuzaki Y. Transcriptional Regulation of Perinatal Lung Maturation. Pediatric clinics of North America 2006;53(5):873-887.
[106] Venkatesh VC, Iannuzzi DM, Ertsey R, Ballard PL. Differential glucocorticoid regulation of the pulmonary hydrophobic surfactant proteins SP-B and SP-C. Am J Respir Cell Mol Biol 1993;8(2):222-8.
[107] Clements J, King R. Composition of the surface active material. In: RG C, editor. The biochemical basis of pulmonary function. New York: Marcel Dekker; 1976. p. 363-387.
[108] Liley HG, White RT, Warr RG, Benson BJ, Hawgood S, Ballard PL. Regulation of messenger RNAs for the hydrophobic surfactant proteins in human lung. J Clin Invest 1989;83(4):1191-7.

[109] Huang HW, Bi W, Jenkins GN, Alcorn JL. Glucocorticoid regulation of human pulmonary surfactant protein-B mRNA stability involves the 3'-untranslated region. Am J Respir Cell Mol Biol 2008;38(4):473-82.

[110] Smith LM, Qureshi N, Chao CR. Effects of single and multiple courses of antenatal glucocorticoids in preterm newborns less than 30 weeks' gestation. J Matern Fetal Med 2000;9(2):131-5.

[111] Guinn DA, Atkinson MW, Sullivan L, Lee M, MacGregor S, Parilla BV, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: A randomized controlled trial. Jama 2001;286(13):1581-7.

[112] Wijnberger LD, Mostert JM, van Dam KI, Mol BW, Brouwers H, Visser GH. Comparison of single and repeated antenatal corticosteroid therapy to prevent neonatal death and morbidity in the preterm infant. Early Hum Dev 2002;67(1-2):29-36.

[113] Uno H, Lohmiller L, Thieme C, Kemnitz JW, Engle MJ, Roecker EB, et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. I. Hippocampus. Brain Res Dev Brain Res 1990;53(2):157-67.

[114] Dunlop SA, Archer MA, Quinlivan JA, Beazley LD, Newnham JP. Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. J Matern Fetal Med 1997;6(6):309-13.

[115] Stewart JD, Gonzalez CL, Christensen HD, Rayburn WF. Impact of multiple antenatal doses of betamethasone on growth and development of mice offspring. Am J Obstet Gynecol 1997;177(5):1138-44.

[116] Ogunyemi D. A comparison of the effectiveness of single-dose vs multi-dose antenatal corticosteroids in pre-term neonates. J Obstet Gynaecol 2005;25(8):756-60.

[117] Rodriguez-Pinilla E, Prieto-Merino D, Dequino G, Mejias C, Fernandez P, Martinez-Frias ML. Antenatal exposure to corticosteroids for fetal lung maturation and its repercussion on weight, length and head circumference in the newborn infant. Med Clin (Barc) 2006;127(10):361-7.

[118] Mazumder P, Dutta S, Kaur J, Narang A. Single versus multiple courses of antenatal betamethasone and neonatal outcome: a randomized controlled trial. Indian Pediatr 2008;45(8):661-7.

[119] Norberg H, Stalnacke J, Heijtz RD, Smedler AC, Nyman M, Forssberg H, et al. Antenatal corticosteroids for preterm birth: dose-dependent reduction in birthweight, length and head circumference. Acta Paediatr 2011;100(3):364-9.

[120] Peltoniemi OM, Kari MA, Hallman M. Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2011;90(7):719-27.

[121] Abbasi S, Hirsch D, Davis J, Tolosa J, Stouffer N, Debbs R, et al. Effect of single versus multiple courses of antenatal corticosteroids on maternal and neonatal outcome. Am J Obstet Gynecol 2000;182(5):1243-9.

[122] Bloomfield F, Knight D, Harding J. Side effects of 2 different dexamethasone courses for preterm infants at risk of chronic lung disease: a randomized trial. J Pediatr. 1998;133(3):395-400.

[123] Mildenhall LF, Battin MR, Morton SM, Bevan C, Kuschel CA, Harding JE. Exposure to repeat doses of antenatal glucocorticoids is associated with altered cardiovascular status after birth. Arch Dis Child Fetal Neonatal Ed 2006;91(1):F56-60.

[124] Mariotti V, Marconi AM, Pardi G. Undesired effects of steroids during pregnancy. J Matern Fetal Neonatal Med 2004;16 Suppl 2:5-7.
[125] Lindahl K, Rubin CJ, Brandstrom H, Karlsson MK, Holmberg A, Ohlsson C, et al. Heterozygosity for a coding SNP in COL1A2 confers a lower BMD and an increased stroke risk. Biochem Biophys Res Commun 2009;384(4):501-5.
[126] Saarela T, Risteli J, Kauppila A, Koivisto M. Effect of short-term antenatal dexamethasone administration on type I collagen synthesis and degradation in preterm infants at birth. Acta PÃ¦diatrica 2001;90(8):921-925.
[127] Korakaki E, Gourgiotis D, Aligizakis A, Manoura A, Hatzidaki E, Giahnakis E, et al. Levels of bone collagen markers in preterm infants: relation to antenatal glucocorticoid treatment. J Bone Miner Metab 2007;25(3):172-8.
[128] Sandesh Kiran PS, Dutta S, Narang A, Bhansali A, Malhi P. Multiple courses of antenatal steroids. Indian J Pediatr 2007;74(5):463-9.
[129] Schaffer L, Luzi F, Burkhardt T, Rauh M, Beinder E. Antenatal betamethasone administration alters stress physiology in healthy neonates. Obstet Gynecol 2009;113(5):1082-8.
[130] Gatelais F, Berthelot J, Beringue F, Descamps P, Bonneau D, Limal JM, et al. Effect of single and multiple courses of prenatal corticosteroids on 17-hydroxyprogesterone levels: implication for neonatal screening of congenital adrenal hyperplasia. Pediatr Res 2004;56(5):701-5.
[131] Ng PC, Wong GW, Lam CW, Lee CH, Fok TF, Wong MY, et al. Effect of multiple courses of antenatal corticosteroids on pituitary-adrenal function in preterm infants. Arch Dis Child Fetal Neonatal Ed 1999;80(3):F213-6.
[132] Owen D, Matthews SG. Glucocorticoids and sex-dependent development of brain glucocorticoid and mineralocorticoid receptors. Endocrinology 2003;144(7):2775-84.
[133] Amin SB, Guillet R. Auditory neural maturation after exposure to multiple courses of antenatal betamethasone in premature infants as evaluated by auditory brainstem response. Pediatrics 2007;119(3):502-8.
[134] Spinillo A, Chiara A, Bergante C, Biancheri D, Fabiana D, Fazzi E. Obstetric risk factors and persistent increases in brain parenchymal echogenicity in preterm infants. Bjog 2004;111(9):913-8.
[135] Spinillo A, Viazzo F, Colleoni R, Chiara A, Maria Cerbo R, Fazzi E. Two-year infant neurodevelopmental outcome after single or multiple antenatal courses of corticosteroids to prevent complications of prematurity. Am J Obstet Gynecol 2004;191(1):217-24.
[136] Liu J, Feng ZC, Yin XJ, Chen H, Lu J, Qiao X. The role of antenatal corticosteroids for improving the maturation of choroid plexus capillaries in fetal mice. Eur J Pediatr 2008;167(10):1209-12.
[137] Liu J, Wang Q, Zhao JH, Chen YH, Qin GL. The combined antenatal corticosteroids and vitamin K therapy for preventing periventricular-intraventricular hemorrhage in premature newborns less than 35 weeks gestation. J Trop Pediatr 2006;52(5):355-9.
[138] Bontis N, Vavilis D, Tsolakidis D, Goulis DG, Tzevelekis P, Kellartzis D, et al. Comparison of single versus multiple courses of antenatal betamethasone in patients with threatened preterm labor. Clin Exp Obstet Gynecol 2011;38(2):165-7.

[139] Nair GV, Omar SA. Blood pressure support in extremely premature infants is affected by different courses of antenatal steroids. Acta Paediatr 2009;98(9):1437-43.
[140] ACOG. ACOG Committee Opinion No. 475: Antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol 2011;117(2 Pt 1):422-4.
[141] Benediktsson R, Lindsay RS, Noble J, Seckl JR, Edwards CR. Glucocorticoid exposure in utero: new model for adult hypertension. Lancet 1993;341(8841):339-41.
[142] Nyirenda MJ, Lindsay RS, Kenyon CJ, Burchell A, Seckl JR. Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. J Clin Invest 1998;101(10):2174-81.
[143] Seckl JR. Physiologic programming of the fetus. Clin Perinatol 1998;25(4):939-62, vii.
[144] Barker DJ. In utero programming of chronic disease. Clin Sci (Lond) 1998;95(2):115-28.
[145] Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295(7):349-53.
[146] Barker D. Mothers, Babies and Disease in Later Life. London: BMJ Publishing.; 1994.
[147] Erhuma A, Salter AM, Sculley DV, Langley-Evans SC, Bennett AJ. Prenatal exposure to a low-protein diet programs disordered regulation of lipid metabolism in the aging rat. Am J Physiol Endocrinol Metab 2007;292(6):E1702-14.
[148] Lazinski MJ, Shea AK, Steiner M. Effects of maternal prenatal stress on offspring development: a commentary. Arch Womens Ment Health 2008;11(5-6):363-75.
[149] Seckl JR. Prenatal glucocorticoids and long-term programming. Eur J Endocrinol 2004;151 Suppl 3:U49-62.
[150] Belkacemi L, Jelks A, Chen CH, Ross MG, Desai M. Altered placental development in undernourished rats: role of maternal glucocorticoids. Reprod Biol Endocrinol 2011;9:105.
[151] Gardner DS, Jackson AA, Langley-Evans SC. Maintenance of maternal diet-induced hypertension in the rat is dependent on glucocorticoids. Hypertension 1997;30(6):1525-30.
[152] Langley-Evans SC. Hypertension induced by foetal exposure to a maternal low-protein diet, in the rat, is prevented by pharmacological blockade of maternal glucocorticoid synthesis. J Hypertens 1997;15(5):537-44.
[153] Dahri S, Snoeck A, Reusens-Billen B, Remacle C, Hoet JJ. Islet function in offspring of mothers on low-protein diet during gestation. Diabetes 1991;40 Suppl 2:115-20.
[154] Pinheiro AR, Salvucci ID, Aguila MB, Mandarim-de-Lacerda CA. Protein restriction during gestation and/or lactation causes adverse transgenerational effects on biometry and glucose metabolism in F1 and F2 progenies of rats. Clin Sci (Lond) 2008;114(5):381-92.
[155] Bellinger L, Langley-Evans SC. Fetal programming of appetite by exposure to a maternal low-protein diet in the rat. Clin Sci (Lond) 2005;109(4):413-20.
[156] Entringer S, Wust S, Kumsta R, Layes IM, Nelson EL, Hellhammer DH, et al. Prenatal psychosocial stress exposure is associated with insulin resistance in young adults. Am J Obstet Gynecol 2008;199(5):498 e1-7.

[157] Entringer S, Kumsta R, Nelson EL, Hellhammer DH, Wadhwa PD, Wust S. Influence of prenatal psychosocial stress on cytokine production in adult women. Dev Psychobiol 2008;50(6):579-87.

[158] Entringer S, Buss C, Kumsta R, Hellhammer DH, Wadhwa PD, Wust S. Prenatal psychosocial stress exposure is associated with subsequent working memory performance in young women. Behav Neurosci 2009;123(4):886-93.

[159] Tang JI, Kenyon CJ, Seckl JR, Nyirenda MJ. Prenatal overexposure to glucocorticoids programs renal 11beta-hydroxysteroid dehydrogenase type 2 expression and salt-sensitive hypertension in the rat. J Hypertens 2011;29(2):282-9.

[160] McArthur S, McHale E, Dalley JW, Buckingham JC, Gillies GE. Altered Mesencephalic Dopaminergic Populations in Adulthood as a Consequence of Brief Perinatal Glucocorticoid Exposure. Journal of Neuroendocrinology 2005;17(8):475-482.

[161] Oliveira Mr, Rodrigues A-Jo, LeÃ£o P, Cardona D, PÃªgo J, Sousa N. The bed nucleus of stria terminalis and the amygdala as targets of antenatal glucocorticoids: implications for fear and anxiety responses. In: Psychopharmacology: Springer Berlin / Heidelberg; 2012. p. 443-453.

[162] Nyirenda MJ, Carter R, Tang JI, de Vries A, Schlumbohm C, Hillier SG, et al. Prenatal programming of metabolic syndrome in the common marmoset is associated with increased expression of 11beta-hydroxysteroid dehydrogenase type 1. Diabetes 2009;58(12):2873-9.

[163] Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 1962;14:353-62.

[164] Erhuma A, Bellinger L, Langley-Evans SC, Bennett AJ. Prenatal exposure to undernutrition and programming of responses to high-fat feeding in the rat. Br J Nutr 2007;98(3):517-24.

[165] Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. Am J Clin Nutr 1999;69(2):179-97.

[166] Waterland RA, Jirtle RL. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition 2004;20(1):63-8.

[167] Csaba G. Phylogeny and ontogeny of hormone receptors: the selection theory of receptor formation and hormonal imprinting. Biol Rev Camb Philos Soc 1980;55(1):47-63.

[168] Berney DM, Desai M, Palmer DJ, Greenwald S, Brown A, Hales CN, et al. The effects of maternal protein deprivation on the fetal rat pancreas: major structural changes and their recuperation. The Journal of Pathology 1997;183(1):109-115.

[169] Langley-Evans SC, Welham SJ, Jackson AA. Fetal exposure to a maternal low protein diet impairs nephrogenesis and promotes hypertension in the rat. Life Sciences 1999;64(11):965-974.

[170] Dietert RR, Lee JE, Olsen J, Fitch K, Marsh JA. Developmental immunotoxicity of dexamethasone: comparison of fetal versus adult exposures. Toxicology 2003;194(1-2):163-76.

[171] Lorenzen JM, Martino F, Thum T. Epigenetic modifications in cardiovascular disease. Basic Res Cardiol 2012;107(2):1-10.

[172] Hussain N. Epigenetic Influences That Modulate Infant Growth, Development, and Disease. Antioxid Redox Signal 2012.
[173] Bird A. DNA methylation patterns and epigenetic memory. Genes Dev 2002;16(1):6-21.
[174] Burdge GC, Hanson MA, Slater-Jefferies JL, Lillycrop KA. Epigenetic regulation of transcription: a mechanism for inducing variations in phenotype (fetal programming) by differences in nutrition during early life? Br J Nutr 2007;97(6):1036-46.
[175] Bertram C, Trowern AR, Copin N, Jackson AA, Whorwood CB. The maternal diet during pregnancy programs altered expression of the glucocorticoid receptor and type 2 11beta-hydroxysteroid dehydrogenase: potential molecular mechanisms underlying the programming of hypertension in utero. Endocrinology 2001;142(7):2841-53.
[176] Burns SP, Desai M, Cohen RD, Hales CN, Iles RA, Germain JP, et al. Gluconeogenesis, glucose handling, and structural changes in livers of the adult offspring of rats partially deprived of protein during pregnancy and lactation. J Clin Invest 1997;100(7):1768-74.
[177] Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. J Nutr 2005;135(6):1382-6.
[178] Lillycrop KA, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br J Nutr 2007;97(6):1064-73.
[179] Weaver IC, Meaney MJ, Szyf M. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. Proc Natl Acad Sci U S A 2006;103(9):3480-5.
[180] Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 2008;3(2):97-106.
[181] Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol 2005;288(1):R34-8.
[182] Terzolo M, Allasino B, Bosio S, Brusa E, Daffara F, Ventura M, et al. Hyperhomocysteinemia in patients with Cushing's syndrome. J Clin Endocrinol Metab 2004;89(8):3745-51.
[183] Langley-Evans SC, Phillips GJ, Benediktsson R, Gardner DS, Edwards CR, Jackson AA, et al. Protein intake in pregnancy, placental glucocorticoid metabolism and the programming of hypertension in the rat. Placenta 1996;17(2-3):169-72.
[184] Stewart PM, Rogerson FM, Mason JI. Type 2 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid and activity in human placenta and fetal membranes: its relationship to birth weight and putative role in fetal adrenal steroidogenesis. Journal of Clinical Endocrinology & Metabolism 1995;80(3):885-90.
[185] McCalla CO, Nacharaju VL, Muneyyirci-Delale O, Glasgow S, Feldman JG. Placental 11 beta-hydroxysteroid dehydrogenase activity in normotensive and pre-eclamptic pregnancies. Steroids 1998;63(10):511-5.

[186] McTernan CL, Draper N, Nicholson H, Chalder SM, Driver P, Hewison M, et al. Reduced Placental 11 Beta-Hydroxysteroid Dehydrogenase Type 2 mRNA Levels in Human Pregnancies Complicated by Intrauterine Growth Restriction: An Analysis of Possible Mechanisms. Journal of Clinical Endocrinology & Metabolism 2001;86(10):4979-4983.

[187] Kitanaka S, Tanae A, Hibi I. Apparent mineralocorticoid excess due to 11 beta-hydroxysteroid dehydrogenase deficiency: a possible cause of intrauterine growth retardation. Clin Endocrinol (Oxf) 1996;44(3):353-9.

[188] Martinerie L, Pussard E, Meduri G, Delezoide AL, Boileau P, Lombes M. Lack of renal 11 Beta-hydroxysteroid dehydrogenase type 2 at birth, a targeted temporal window for neonatal glucocorticoid action in human and mice. PLoS One 2012;7(2):e31949.

[189] Wyrwoll CS, Mark PJ, Waddell BJ. Developmental programming of renal glucocorticoid sensitivity and the renin-angiotensin system. Hypertension 2007;50(3):579-84.

[190] Ferrari P, Lovati E, Frey FJ. The role of the 11beta-hydroxysteroid dehydrogenase type 2 in human hypertension. J Hypertens 2000;18(3):241-8.

[191] Basta-Kaim A, Budziszewska B, Leskiewicz M, Fijal K, Regulska M, Kubera M, et al. Hyperactivity of the hypothalamus-pituitary-adrenal axis in lipopolysaccharide-induced neurodevelopmental model of schizophrenia in rats: effects of antipsychotic drugs. Eur J Pharmacol 2011;650(2-3):586-95.

[192] Erhuma A, McMullen S, Langley-Evans SC, Bennett AJ. Feeding pregnant rats a low-protein diet alters the hepatic expression of SREBP-1c in their offspring via a glucocorticoid-related mechanism. Endocrine 2009;36(2):333-8.

[193] Shimomura I, Hammer RE, Richardson JA, Ikemoto S, Bashmakov Y, Goldstein JL, et al. Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. Genes & Development 1998;12(20):3182-3194.

[194] Horton JD, Shimomura I, Ikemoto S, Bashmakov Y, Hammer RE. Overexpression of sterol regulatory element-binding protein-1a in mouse adipose tissue produces adipocyte hypertrophy, increased fatty acid secretion, and fatty liver. J Biol Chem 2003;278(38):36652-60.