Chapter 9
Developmental Consequences of Prenatal Administration of Glucocorticoids in Rodents and Primates

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Abstract Since their first use in 1972 by Liggins and Howie, prenatal exposure to synthetic glucocorticoids (GCs) is commonplace in antenatal medicine to impede the preterm birth-associated morbid symptoms. Synthetic GCs are ligands of the receptor of endogenous GC, the glucocorticoid receptor. Although prenatal GC is warranted for its increased survival rate of preterm infants, the repeated exposure to synthetic GC long-term effects has been questioned, and investigation of potentially harmful long-term effects in animal studies is required. I will first summarise the existing findings in animal studies, which include two robust phenotypes: a transient reduction of body weight and alteration of the hypothalamo–pituitary–adrenal gland axis activity. Several studies assessed the neurotransmitters' concentrations in animals exposed to prenatal GC and reported an overall increased activity of serotoninergic and dopaminergic systems. Prenatal GC administration has also been shown to increase anxiety and reduce cognitive abilities in the long term. All these effects have been proposed to be mediated via epigenetics programming, which is the change of gene expression caused by mechanisms other than the DNA sequence (e.g. promoter methylation). Interestingly, the same mechanism has been proposed to mediate the long-term effects of altered maternal behaviour, suggesting that the developing individual, from conception until weaning, is undergoing epigenetics programming based on its environment.

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9.1 Why Study Prenatal Synthetic Glucocorticoids?

In the USA, 7–10% of births are premature (before 37th gestational week) each year (N.I.H. Consensus 1994), and preterm birth is the leading cause of neonatal death (Mathews and MacDorman 2011). Prenatal synthetic glucocorticoids (GC) are commonly prescribed in diagnosed preterm delivery to prophylactically impede the associated morbid symptoms (e.g. respiratory distress syndrome and intraventricular haemorrhage, Liggins and Howie 1972). This treatment received support from the American National Institutes of Health (NIH) that stated in the 1994 Consensus Developmental Conference on the Effects of Corticosteroids for Fetal Maturation on Perinatal Outcomes: "All fetuses between 24 and 34 weeks' gestation at risk of preterm delivery should be considered candidates for antenatal treatment with corticosteroids" (N.I.H. Consensus 1994). The positive impact of prenatal GC treatment on preterm baby survival has been confirmed in a recent meta-analysis (Crowther et al. 2011). The efficacy of prenatal GC has been observed for birth occurring within 7 days post treatment (Roberts et al. 2006), and consequently it is common practice in clinics to repeat the treatment weekly from diagnosis until birth (Crowther et al. 2011). The positive effects associated with prenatal GC exposure have however been mitigated by reports of transient reduction in some growth indices (mean weight, mean length and mean *Z*-scores of head circumference) (Crowther et al. 2011) and other unwanted side effects (e.g. increased behavioural and hormonal responses to painful stimuli, Davis et al. 2011). In a recent review focusing on the effects of prenatal GC on the hypothalamo–pituitary–adrenal gland axis (HPA), Tegethoff et al. (2009) concluded that antenatal GC exposure resulted in reduced basal and challenged HPA activity visible from foetal developmental stage up to 2 weeks of age. These effects were more marked with increasing total amount of antenatal GC, suggesting a dose response type of effects. Because this prenatal GC treatment has only been recently adopted in clinical practice and because of the difficulty to follow-up treated infants beyond hospital discharge, there are very few long-term studies of subjects exposed to prenatal GC. These studies reported no differences in neurosensory functions at 6 months (Mazumder et al. 2008) or, in the Kaufman assessment battery for children—which provides an IQ equivalent—at 5 years (Foix-L'Helias et al. 2008). To account for the evolving practice of prenatal GC treatment, the NIH revisited the Consensus of 1994 in 2001 and one of their conclusion was "animal studies should evaluate the pathophysiologic and metabolic mechanisms of potential benefits and risks, including the effects of repeat corticosteroids on central nervous system myelination and brain development" (N.I.H. Consensus 2001).

9.2 Stress, the HPA Axis and Their Relation to Synthetic GC

A stressor has been defined by Cannon as a situation of threat to an organism, to which it will react with physiological responses, aiming at energy mobilisation and increase in arousal, that increase survival through either confrontation or avoidance,

the so-called fight-or-flight response (Cannon 1939). This definition has been refined by several authors and most recently by McEwen (McEwen and Wingfield 2003) as follows: [stressful stimuli are] "… events that are threatening to an individual and which elicit physiological and behavioural responses as part of allostasis (i.e. maintenance of an organism homeostasis) in addition to that imposed by normal life cycle". The stress response is characterised by a fast activation of the sympathetic branch of the autonomous nervous system (ANS) and by a delayed slower increase of HPA axis activity. ANS activation stimulates the release of catecholamines (epinephrine and norepinephrine) from the adrenal medulla. Following termination of the stressor, the parasympathetic branch of the ANS starts a compensatory response. The slower activation of the HPA axis results in release of the 41 amino acid peptide corticotropin-releasing hormone (CRH, also known as corticotropin-releasing factor and corticoliberin) by the paraventricular nucleus of the hypothalamus. CRH induces in pituitary target cells release of adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal gland, which releases endogenous GC (cortisol in primates, including humans, and corticosterone in rats) in blood flow where it is quickly bound by corticosteroid-binding globulin (CBG, Westphal 1983). Only free GCs are active. The CBG binding of GC serves as a tissue buffer against potential deleterious effects of elevated GC and can regulate the availability of free hormone to target tissue (about 95% of GC is protein bound, Gayrard et al. 1996). Recent findings have proposed a more active role of CBG in terms of mediation of the availability of GC to specific target tissue, as opposed to just reservoir of GC, as well as intracellular transportation of bound GC in specific cell types, allowing increased free GC levels above what could be achieved through simple diffusion (reviewed in Breuner and Orchinik 2002). The HPA axis activity is returned to baseline via a negative feedback mechanism that acts at all of its three levels: the hypothalamus, the pituitary and the adrenal gland (see Fig. 9.1 for a general schematic of the HPA axis function).

GC binds to both glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) (Rosenfeld et al. 1993; de Kloet et al. 1990). Ontogeny of GR and MR in the rodent foetal brain undergoes spatial, temporal and sex-specific regulations (Owen and Matthews 2003; Pryce 2008), but both receptors are visible from respectively embryonic days 15.5 and 12.5 (Diaz et al. 1998). In humans, MR and GR are expressed in hippocampus from gestational week 24 (Noorlander et al. 2006). MR and GR are ligand-activated intracytoplasmatic transcription factor composed of three domains: the N-terminal domain (GR reviewed in Wright et al. 1993, MR reviewed in Pascual-Le Tallec and Lombes 2005), responsible for transcriptional activity; the DNA-binding domain; and the C-terminal domain or ligand-binding domain (LBD). Upon binding of their ligand, GR and MR translocate to the nucleus, dimerise and recognise specific semi-palindromic DNA promoter segments; this enables direct and indirect interactions with the transcription initiation complex and thereby the upregulation of target gene expression (reviewed in Beato and Sanchez-Pacheco 1996). Additional mechanisms mediated through ligand-bound receptors can repress transcription of certain genes: binding to a negative response elements (Malkoski and Dorin 1999), heterodimerisation with other nuclear receptors

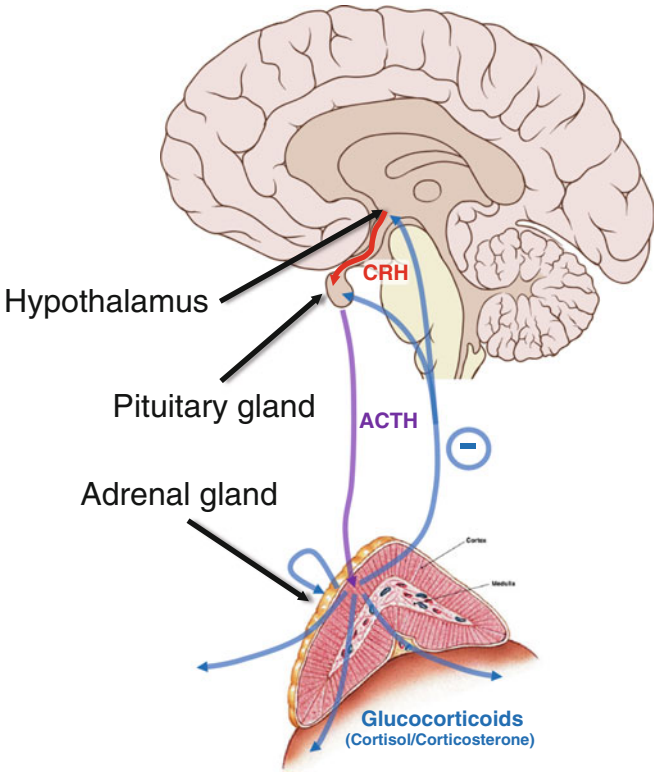

Fig. 9.1 Schematic of the HPA axis. In response to a stressor, the hypothalamus secretes CRH (*red*), which stimulates secretion of ACTH (*violet*) by the pituitary gland. ACTH in turn activates the adrenal gland release of GC (*blue*). GC exerts a negative feedback at all three levels

(Ou et al. 2001) or cross-talk with other nuclear receptors through protein–protein interactions (McKay and Cidlowski 1998, 1999, 2000). In addition to these well-studied transcriptional effects of GC, recent publications have reported the following non-genomic effects (Song and Buttgereit 2006): (1) physiochemical interaction with cellular membrane (Buttgereit and Scheffold 2002), (2) membrane-bound GR-mediated non-genomic effects (Groeneweg et al. 2011) and (3) cytosolic GR-mediated non-genomic effects (Bartholome et al. 2004).

The two main synthetic GCs are dexamethasone (DEX) and betamethasone (BETA), which differ from the endogenous GC by a fluorine atom on the ninth carbon. Due to the structural differences between endogenous and synthetic GCs, the latter exhibit increased binding to GR (25-fold endogenous GC affinity) and strongly reduced binding to MR (Grossmann et al. 2004). There are other differences between synthetic and endogenous GC: (1) The 11β-HSD2 enzyme oxidises natural GC to their inactive metabolite; it has been reported in numerous tissues, especially in the placental syncytiotrophoblast, where it provides a good protection of the foetus from maternal GC (Speirs et al. 2004). Synthetic GCs are poor substrates for

11β-HSD2; therefore they readily cross placenta and access the foetus (Gitau et al. 2001; Murphy et al. 2007). After 1 h incubation, 95% of endogenous GC but only 17% of synthetic GC is metabolised by 11β-HSD2 (Brown et al. 1996). (2) Contrarily to the natural GC, which activity can be modulated by their binding to CBG, synthetic GCs do not bind by CBG and only partially to albumin; 65–70% of synthetic GC is in bound state compared to the 95% of endogenous GC (Peets et al. 1969; Schwab and Klotz 2001). Synthetic GC exposure reproduces some elements of the GR activation following stress response; however, note the following differences between this treatment and the stress response: absence ANS stimulation, metabolisation by 11β-HSD2, low to no MR activation and different bioavailability of synthetic GC.

9.3 Summary of the Known Effects of Prenatal GC in Animal Models

Most studies assessing prenatal synthetic GC exposure used rodents (rats, guinea pigs and mice); there were also a few studies that used non-human primates or ovine, which focused on the HPA axis activity and lung functions. Studies in rodents typically used a treatment of 0.1 mg/kg during the last week of pregnancy (gestational days 14–21). In primates, treatment was usually performed in the last trimester of pregnancy; however, there were no general rules for the treatment duration or dose, which varied respectively from 2 to 42 days and from 0.1 to 15 mg/kg (Coe and Lubach 2005). The foetal treatment used in all these studies varied from subclinical exposure, in dose and duration, to overexposure. It is very difficult to select the onset, duration and dose of treatment, as there are differences in response to GC between species. Furthermore, organ- or system-specific developmental stages might be different at the same relative gestational age between precocial (primates) and altricial (rat) species. The only common element visible across studies and across species is that the onset of the treatment was systematically targeting the last trimester of pregnancy.

An extensive number of animal studies examined the impact of prenatal GC exposure on physical growth and HPA axis function. Prenatal synthetic GC has been associated with a reduction of body weight throughout life in rats (Brabham et al. 2000; Emgard et al. 2007; Hauser et al. 2006, 2009; Oliveira et al. 2006; Welberg et al. 2001), although some studies using lower synthetic GC doses have reported catch up growth (Kreider et al. 2005; McArthur et al. 2005). This effect was not observed in primates (Hauser et al. 2007, 2008; Uno et al. 1994), except in two studies using longer treatment (Johnson et al. 1981; Novy and Walsh 1983). In rodents, the general findings were that HPA basal activity was unaffected whereas its response to a stressful situation was increased by prenatal GC (Brabham et al. 2000; Hauser et al. 2009; Oliveira et al. 2006; Bakker et al. 1995; Hougaard et al. 2005; Muneoka et al. 1997; Shoener et al. 2006). Two studies reported a reduction of GR in the hippocampus in response to prenatal GC

exposure (Brabham et al. 2000; Welberg et al. 2001), which could mediate the increased reactivity to the stressor via a reduction of the sensitivity of hippocampus to the negative feedback of GC. In guinea pigs, prenatal synthetic GC exposure had a sexual dimorphic effect on HPA axis activity. In males, the HPA axis response to stress was increased, whereas in females, the effect was modulated by the hormonal cycle. In the follicular early luteal phase it resulted in increased basal and challenged HPA axis activity, but this was reversed in the late luteal phase (Liu et al. 2001). In a long-term follow-up study of lamb exposed to prenatal GC, Sloboda and colleagues reported that the HPA axis exhibited no changes at 6 months, increased basal and challenged activity at 1 year and decreased basal and challenged activity at 3 years of age (Sloboda et al. 2000, 2002, 2007). This clearly underlines the importance of long-term follow-up studies as it suggests that prenatal GC might have effects that are age-dependent. Both in rhesus and vervet monkeys, challenged HPA axis activity was increased following prenatal synthetic GC treatment (Uno et al. 1994; de Vries et al. 2007), and this effect was also observed in basal activity in rhesus monkey. However, there was no evidence of impact on HPA axis activity in marmoset monkey offspring exposed to prenatal GC (Hauser et al. 2007). In conclusion, the challenged HPA axis activity is increased in most animal models after prenatal GC treatment; a similar increase in activity was reported in young infants (Tegethoff et al. 2009). The findings on basal activity seem to be more variable among studies. There is a strong interaction between the effects of prenatal GC treatment on HPA axis activity and the sex of the subjects in rats (Brabham et al. 2000; Hauser et al. 2009) and in guinea pigs (Liu et al. 2001). Although a similar sexual dimorphism was not reported in primate studies, it is noteworthy here to highlight that most primate studies only used males or were not able to account for the sex due to the limited number of subjects in these studies. In two studies both male and female marmoset monkeys were assessed for HPA axis activity and no differences were reported (Hauser et al. 2007, 2008).

A few studies focused on neurotransmitter changes in rodents. A general increase in serotoninergic function can be assumed, as prenatal synthetic GC promotes serotonin transporter expression in brainstem (Slotkin et al. 1996) and reduces serotonin turnover in hypothalamus, neocortex, hippocampus and midbrain as well as increases serotonin in hypothalamus and midbrain (Muneoka et al. 1997). Kreider et al. (2005) reported an increased cholinergic synaptic activity in the hippocampus of male rats. Prenatal GC results in an increase of tyrosine hydroxylase immunopositive cell counts in the substantia nigra pars compacta and an increase of dopamine in the dorsolateral striatum (McArthur et al. 2005), suggesting that this treatment results in an increased dopaminergic activity.

Finally, several studies investigated behavioural long-term effects of prenatal synthetic GC. In rodents, this treatment decreases locomotor activity and increases anxiety (Oliveira et al. 2006; Welberg et al. 2001), but there are also reports of increased locomotor activity (Muneoka et al. 1997) as well as reduced anxiety (Velisek 2006). The impact of prenatal GC treatment on learning was assessed most frequently in the Morris water maze (MWM). The MWM is the most commonly

used behavioural task to assess spatial learning in rodents. It consists of a circular pool filled with cold water, in which a hidden escape platform is positioned. Learning is assessed by the reduction of latency to find the platform. Prenatal GC was reported to yield a general impairment of performance in this task (Brabham et al. 2000; Emgard et al. 2007; Kreider et al. 2005), although one study failed to replicate this effect (Oliveira et al. 2006). Noteworthy here, a study using cross-fostering showed that this reported deficit in spatial learning might not be mediated by the prenatal GC treatment but by the associated increased maternal care (Hauser et al. 2009). Cross-fostering consists of fostering treated and control pups to treated and control surrogate mother, resulting in litters composed of half-treated half-control pups reared either by treated or control dams. Learning was also assessed following prenatal GC in the eight-arm radial maze, a task in which the animal has to get a reward from each arm, re-entry in an arm already visited being an error. Prenatal GC treatment resulted in a quicker learning in males and in performance impairment in females (Kreider et al. 2005). In a set of two studies, we evaluated the possible association between prenatal GC exposure and symptoms of two psychiatric diseases, schizophrenia and depression. Rat offspring exposed to prenatal GC did not exhibit any alteration of prepulse inhibition or latent inhibition (Hauser et al. 2006), which respectively accounts for schizophrenia-induced disruption in sensory motor gating (Braff et al. 1992) and the ability to ignore irrelevant stimuli (Baruch et al. 1988). We also failed to obtain evidence of depressive-like behavioural performance in paradigm taxing processes affected by depression, namely anhedonia and behavioural despair (Hauser et al. 2009). Anhedonia was assessed using the progressive ratio schedule of reinforcement, a task in which the subject has to increase progressively the workload required to obtain a reward, with a reduction of maximum workload reached modelling anhedonia. Behavioural despair was assessed using the Porsolt forced swim task and in unconditioned stimulus pre-exposure in active avoidance. In both tasks the subject is exposed to an inescapable aversive situation (cold water in Porsolt and foot shocks in active avoidance), with reduced latency to stop escape attempts modelling behavioural despair. These findings confirmed and extended the existing report of unaffected performance in the Porsolt forced swim test following prenatal GC (Oliveira et al. 2006). In primates, we assessed the impact of prenatal GC on motor learning using an adaptation of Whishaw skilled reaching task for rats and discrimination learning and motivation for a palatable reward using the Cambridge Neuropsychological Test Automated Battery (CANTAB) system (Hauser et al. 2008). In the skilled reaching task, the subject has to reach through a narrow opening for a palatable reward. The CANTAB apparatus consists of a programmable touch screen. We assessed discrimination learning by rewarding only one out of two presented stimuli; once good performance was reached the rewarded and unrewarded stimuli were reversed to assess reversal learning. Motivation was assessed in a progressive ratio schedule of reinforcement. Marmosets exposed to GC during the last third of pregnancy showed no improvement of performance in the skilled reaching task with experience and an improvement of reversal learning, but no changes in motivation and no other effects were observed.

9.4 Mediation of Effects of Prenatal Synthetic GC Exposure in Adulthood

The first mediator that comes to mind for long-term effects of prenatal synthetic GC exposure is a major alteration of development (e.g. reduction of organ size, change in the differentiation of specific subpopulation of cells). Prenatal synthetic GC has only shown a transient reduction of birth weight in rodents (Hauser et al. 2006; Kreider et al. 2005; McArthur et al. 2005; Muneoka et al. 1997; Burlet et al. 2005), an effect that was not visible in primates (Hauser et al. 2008) except in studies using especially long treatments and/or high concentration of GC (Johnson et al. 1981; Novy and Walsh 1983). In addition, these studies with longer treatment duration reported decreased hippocampus size as well as reduced number of pyramidal and granule neurons. This indicates that the effects of prenatal GC treatment on physical growth and CNS development follow a dose-dependent curve. A similar dose-dependent effect of prenatal GC treatment on HPA axis activity was reported in human babies (Tegethoff et al. 2009). In clinical studies, the general outcome of prenatal synthetic treatment is also a transient reduction of birth weight, which is recovered after few days (Crowther et al. 2011; French et al. 1999). Considering these transient effects and the absence of other major defect at birth, major developmental effects resulting in abnormal organs following prenatal synthetic GC treatment are unlikely with the dose range used in clinics or in most animal studies. The reduced birth weight reported rather seems to represent the known effects of GC, namely growth reduction in favour of an increased maturation. Thus the low dose and short treatment used in clinics do not result in major alteration of development. Interestingly, increasing dose or duration of treatment was shown to have dramatic impact on survival in animal models. In a pilot study in rats, we observed that increasing the typical prenatal synthetic GC doses used in this species by twofold resulted in major developmental problem, with most of the litter being either stillborn or having major malformation leading to early life death (Hauser et al. unpublished results). A similar report was published in primates reporting an increased number of stillbirths following high-dose prenatal GC treatment (Novy and Walsh 1983).

The next most plausible mediator candidate is prenatal or foetal programming; it is the phenomenon by which a specific adulthood phenotype is set up based on foetal environment. Barker (Hales and Barker 2001) made the first proposition of prenatal programming by associating prenatal undernutrition with several adulthood diseases (including but not limited to metabolic syndrome, type 2 diabetes) in his thrifty phenotype hypothesis. In this hypothesis, prenatal undernutrition is perceived by the foetus, which consequentially adapts its development (e.g. via increased food storage in fat tissue). Barker highlighted that such beneficial strategy would be harmful to the offspring if their future environment was not under food restriction. The HPA axis has also been proposed to undergo prenatal programming. It is known that a stressful environment (pathogens, nutrient deprivation, high predation, etc.) results in increased HPA activity in the pregnant mother. In response to that, the foetus development is adapted and the offspring exhibit increased basal and challenged HPA axis activity, decreased GR mRNA and protein levels as well as

behavioural fear and anxiety (Seckl 2001, 2004). This phenotype is more adapted to a threatening environment, and it increases the offspring survival rate despite its cost. As stated by Barker, a major drawback of prenatal programming is that it requires long-term prediction based on the information perceived by the foetus to reliably represent the environment in which the adult offspring will live. The effect of prenatal GC treatment can be interpreted in the frame of this theory as follows: prenatal GC is perceived by the developing foetus as indicator of a stressful environment (due to its activation of the HPA axis); however, this signal is a poor predictor of adulthood environment; thus, the infant will have a maladaptive phenotype in the form of an overreactive HPA axis in a normal environment that will yield no benefits or even be harmful.

The mediation of prenatal programming has yet to be understood; however, several indices suggest that epigeneticss play a major role. Epigenetics is the modification of genetic information over and above alteration in nucleotide sequence. Its control of gene expression is mediated by DNA methylation and/or modification of chromatin packaging (Wolffe 1998). Recent studies support the association between perinatal stress and epigenetics programming of element of the stress response. The laboratory of Meaney presented evidence associating early life variation in maternal care and epigenetics (Weaver et al. 2004). They reported that offspring of dam exhibiting high maternal care had reduced GR exon 1_7 methylation and hippocampal GR expression. Confirming the epigenetics nature of this effect, cross-fostering of these pups resulted in a phenotype that was dependent of the maternal care and not of the genetic parent. Although not in the central nervous system, another study by Thomassin et al. (2001) is supporting the association between prenatal GC treatment and epigenetics. They reported that prenatal levels of GC were modulating the demethylation of the glucocorticoid receptor responsive unit of the tyrosine aminotransferase gene promoter in rat liver. These studies provide the first evidences for a mechanism that could mediate the integration of foetal environment in genetic expression. Thus it seems that prenatal synthetic GC exposure and increased maternal behaviour both lead to epigenetics modification of gene expression in adulthood, not only in the brain but also in other organs. Mediation by epigenetics prenatal programming might therefore be the best way to explain the integration of environmental information and the consequent adapted foetal development, such as the thrifty phenotype in response to undernutrition or the increased stress response observed after prenatal synthetic GC.

9.5 Other Factors Modulating Prenatal GC Treatment Effects

Gender of the exposed foetus and the maternal care it received in early life have repeatedly been reported to modulate the effects of prenatal GC treatment. In the rat prenatal synthetic GC literature, most studies were performed using solely male subjects, while in other species the inclusion of both males and females is more common. Differences between genders are important considering the fact that each gender undergoes a specific prenatal development path from as early as the first week of life

in humans. This differential development between male and female continues postnatally and peaks at puberty, when endocrine and physical differences are accentuated between genders. Thus, for studies trying to achieve highest possible translational value of their findings, the use of both males and females is essential. Considering that there are important endocrine, neurologic and behavioural differences between sexes, the effect of prenatal synthetic GC on any of these could be different between the two genders. The inclusion of both genders in studies requires an increase in number of experimental subject to achieve the necessary statistical power. This can be complicated with primate, which is the reason why in most studies, experimenters either only used males or did not use the sex as a factor in their analyses. In rat studies using both genders, experimenters reported a clear sexual dimorphism of prenatal GC treatment, with increased HPA axis reactivity being restricted to males (Brabham et al. 2000; Hauser et al. 2009). In guinea pig, the effect of prenatal synthetic GC exposure was an increased HPA axis response in males and oestrus cycle dependant in females (Liu et al. 2001). The sexual dimorphism observed in the effects of prenatal GC exposure can have a wide number of mediators; this was not yet fully investigated. An obvious mediator is the sex hormones themselves, particularly when considering the overlap between their activity pathway and the one of GC and the possibility of GR to form heterodimer with sexual hormone receptors.

Prenatal exposure to synthetic GC has been shown to result in altered maternal behaviour in rodents (Brabham et al. 2000; Hauser et al. 2009) and in altered infant home cage behaviours in primates (Hauser et al. 2008). Manipulations affecting maternal behaviour (e.g. early deprivation or early manipulation) have been shown to alter HPA axis activity as well as behavioural response in various tasks in adult rodents of the first as well as the second generation (Pryce and Feldon 2003; Iqbal et al. 2012) and primates (Pryce et al. 2011). It is therefore possible that part of the effects attributed to prenatal synthetic GC treatment could originate from the altered maternal behaviour. To be able to dissociate direct effects of prenatal synthetic GC treatment from indirect effects mediated via altered maternal behaviour, the best strategy is to use a cross-fostering design. Despite the increase in number of animals needed, the possibility to dissociate effects mediated via the treatment from those due to altered maternal behaviour is a considerable advantage in terms of data interpretation. An example where such refinement proved to be critical is the impact of prenatal synthetic GC on spatial learning. In the MWM, prenatal GC exposure was reported to result in a decrease of performance (Emgard et al. 2007). However this finding was reinterpreted after a study using a cross-fostering design reported that the decreased performance was due to the alteration of maternal behaviour associated with this treatment (Hauser et al. 2009).

9.6 Conclusions

There is no doubt that the use of prenatal GC is necessary in diagnosed preterm delivery, as this treatment clearly improves survival rate of newborn. Nevertheless, it is important to understand all the possible long-term effects such a treatment

could yield and thereby develop better strategy to accommodate them. GCs are the key hormones of the HPA axis and inhibit growth; it is therefore not surprising that most clinical studies focused on the HPA axis and on physical growth of infants exposed to prenatal GC treatment. The general finding in this regard was that prenatal GC treatment results in a transient sensitisation of the HPA axis and a transient reduction of infant weight. The transient character of these effects is questioned by studies performed in animals, especially considering the life-long sensitisation of the HPA axis reported in rats. A long-term follow-up study in lamb showed that the impact of prenatal GC on HPA axis was age dependent. In regard of body weight, although most animal studies reported only a transient effect of prenatal GC treatment, there is at least one report of long-lasting effects in rats (Hauser et al. 2006). This highlights the importance to obtain a long-term follow-up study in humans, as the effect on HPA axis and/or body weight could remain silent until a certain age. On the background of these physiological changes, there were only few long-term effects of prenatal GC on cognition and behavioural performance in various tasks. This absence of long-term behavioural effects is positive considering the worries regarding side effects of this treatment in clinics. A very interesting finding obtained in rodent studies is that some of the effects traditionally attributed to prenatal GC treatment were shown to be mediated by the increased maternal care of dams receiving GC. First of all, this finding highlights the importance to use a cross-fostering design when investigating any perinatal treatment, to be able to dissociate the direct effect from those mediated via the mother. Based on these observed long-term effect of prenatal GC exposure mediated via alteration of maternal behaviour in rats, clinical investigation focusing on such possibilities in humans are highly warranted.

Epigenetics programming seems to be the mediator of both prenatal synthetic GC exposure and alteration of maternal behaviour. Accordingly, prenatal and early life programming could be reunited into one longer process: developmental epigenetics programming. Using this mechanism, growing organisms could adapt their development strategy according to modifications of their environment perceived either directly or indirectly. This hypothesis provides an elegant common mechanism to integrate information from the various life stages to have a continuous development adapted to the environment. While, natural selection works over generations and selects phenotypes according to long-term variation of the environment, developmental epigenetics programming provides a faster mechanism to adapt to rapid environmental changes. Because any environment will indeed present both fast and slow changes, it would be expected that organisms developed mechanisms to integrate both of them in their development to achieve the most adapted phenotype. The quickness of the developmental epigenetics programming is also responsible for its drawback, namely the risk of maladaptation, when a signal is not reliably representing the environment in which the developing organism will be in its adult life. Thus while developmental epigenetics programming compensates natural selection to accommodate fast environmental changes, natural selection slower process might compensate for the risk of maladaptation existing in developmental epigenetics programming. These two mechanisms would thereby act in

synergy to achieve the best phenotype according to long-term selection and short-term adaptation.

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