Glucocorticoid Programming in Very Preterm Birth

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Introduction

The ‘fetal cortisol hypothesis’ was postulated in 1993 as an explanation for the association between low birth weight and certain chronic diseases, such as cardiovascular diseases and diabetes mellitus type 2 (DM2) [1]. In brief, it was hypothesized that abnormally low activity of the placental barrier enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2 allows a larger proportion of maternal cortisol to reach the fetus, resulting in intrauterine growth restriction (IUGR), increased hypothalamus-pituitary-adrenal (HPA) axis activity and predisposition to hypertension and DM2. In support of this hypothesis, in a variety of animal models, birth weight was reduced by prenatal exposure to dexamethasone, which escapes inactivation by 11β-HSD type 2 [2]. The offspring exhibited persistent increases in HPA axis activity, blood pressure, glucose intolerance and anxiety-like behavior [2]. In line with animal experiments, studies in humans showed that prenatal exposure to maternal anxiety or depression, by exposure of the fetus to excess glucocorticoids, was associated with a similar phenotype [2]. Furthermore, children born to mothers who regularly consumed liquorice – a potent inhibitor of 11β-HSD type 2 – during their pregnancies had greater HPA axis activity, reduced per-
formance at several cognitive tasks and more externalizing behavior [3, 4].

Reduced 11β-HSD type 2 activity has also been implicated to play a role in the length of gestation. Two independent studies found that heavy use of liquorice was associated with shorter gestation [5, 6]. Others found that the expression and activity of 11β-HSD type 2 were reduced in the placentas of mothers with known risk factors for preterm delivery, such as preeclampsia and IUGR [7, 8].

In healthy pregnancies, the fetal HPA axis is still immature in the third trimester, and in pathological pregnancies this may even be more evident because of the suppressive effects of excess maternal cortisol [9]. Therefore, it is of no surprise that the HPA axis is not fully functional among preterm infants in their first weeks of life; a proportion of them manifest clinical signs of adrenocortical insufficiency [10]. Conversely, later in life, survivors show features of increased glucocorticoid bioactivity, such as abdominal fat distribution, raised blood pressure, insulin resistance and DM2 [11–15]. This poses the question as to whether the HPA axis could also be programmed postnatally by adversities associated with preterm birth.

**Glucocorticoids and Resilience to Neonatal Threats**

Worldwide, of all live-born children, 11.1% (range: 5–18%) are born prematurely (i.e., <37 weeks of gestation) [16]. Approximately 1–2% of all babies are born very preterm (i.e., <32 weeks) [17, 18], necessitating admission to a neonatal intensive care unit (NICU). In this review, we will focus specifically on the latter group. Although pregnancy dating can be reliably assessed with ultrasound these days, birth weight is still being used as a surrogate for gestational age by many studies. Therefore, we also included studies in infants with very low birth weight (VLBW; i.e., <1,500 g) or extremely low birth weight (ELBW; i.e., <1,000 g).

Owing to improvements in neonatal care, the chances for survival of infants born between 26 and 32 weeks of gestation have improved from 70% in the early 1980s to more than 90% nowadays [19]. The limit of viability has been set at 22–24 weeks. Overall, infants born at the threshold of viability experience a more complicated neonatal course and, consequently, carry much higher risks of neonatal mortality and long-term morbidities [20].

Cortisol is necessary for the maintenance of both blood pressure and glucose homeostasis. It influences the sensitivity of the peripheral tissues to the actions of insulin, glucagon and catecholamines. Other mechanisms of action include inhibition of nitric oxide-induced vasodilation, inhibition of vasodilator prostanoids, upregulation of angiotensin II receptors and, at higher concentrations, activation of renal mineralocorticoid receptors [21].

Hypotension is a common threat during the early postnatal course of very preterm infants. Among the causes of hypotension are abnormalities in the regulation of the vascular tone (e.g., by sepsis or adrenocortical insufficiency), left-to-right shunting through a persistent ductus arteriosus, volume depletion and myocardial dysfunction [22, 23]. Although systemic hypotension has been associated with adverse neurological outcome, it is unclear whether low blood pressure alone, in the absence of other signs of hemodynamic instability, is harmful for the very preterm infant’s brain [22, 23].

Hypoglycemic episodes are frequently observed in the early postnatal course of very preterm infants. Acute illnesses, such as the respiratory distress syndrome, infections and necrotizing enterocolitis, and asphyxia increase the glucose demands in tissues. The endogenous glucose production can only partly compensate for sudden declines in the circulating glucose level [24], attributable to low hepatic glycogen content [25], poor availability of the gluconeogenic substrates alanine and glycerol [26], impaired glucose-6-phosphatase activity (the final step in both glycolysis and gluconeogenesis) [27] and a reduced capacity to secrete counter-regulatory hormones like cortisol [28, 29]. Also lipolysis and ketogenesis are severely impaired, even at low blood glucose levels [26, 30].

Relative adrenal insufficiency is common among very preterm infants in their first weeks of life and occurs when the HPA axis is unable to produce sufficient cortisol for the degree of illness. However, there is lack of consensus about the definition of a normal cortisol value. A cortisol level ≥15 μg/dl (i.e., ≥414 nmol/l) has been considered adequate for ill very preterm infants [29]. According to this definition, a considerable proportion fail to mount an adequate adrenocortical response to stress (table 1). Still, their cortisol levels are higher than in healthy fetuses of the same postconceptual age [31]. Infants with ELBW who had a cortisol level in the upper quartile at postnatal days 5–7 were found to be at risk of brain damage [32].

Multiple levels along the HPA axis might be affected in infants born preterm (table 1). First, several studies demonstrated that the pituitary response to exogenous corticotropin-releasing hormone (CRH) was impaired [33–36] when an adrenocorticotropic hormone concentration of
<table>
<thead>
<tr>
<th>First author [Ref.], year</th>
<th>n</th>
<th>Characteristics of participants</th>
<th>Age at assessment</th>
<th>Measurements</th>
<th>Group</th>
<th>Cortisol (nmol/l)</th>
<th>ACTH (pmol/l)</th>
<th>Other findings</th>
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<td><strong>No stimulation test</strong></td>
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<tr>
<td>Doerr [40], 1988</td>
<td>20</td>
<td>Preterm group: 33–36 weeks,</td>
<td>2, 6, 12 and</td>
<td>Basal cortisol,</td>
<td>Preterm</td>
<td>Between 87±29^a</td>
<td>n.a.</td>
<td>↑17-OHP, aldosterone and B during first week of life in preterm compared to term group</td>
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<tr>
<td></td>
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<td>healthy (n = 8) Term group:</td>
<td>24 h, 4 and 7</td>
<td>aldosterone, 17-OHP, progesterone, S, DOC, B and E</td>
<td></td>
<td>at 7 days and 267±107^a at 12 h</td>
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<td></td>
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<td>healthy (n = 12)</td>
<td>days</td>
<td></td>
<td>Term</td>
<td>Between 75±33^a</td>
<td>n.a.</td>
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<td></td>
<td>at 24 h and 288±71^a at 2 h</td>
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<tr>
<td>Lee [41], 1989</td>
<td>38</td>
<td>Preterm group: 31–35 weeks,</td>
<td>2–5 days</td>
<td>Basal cortisol,</td>
<td>Preterm sick</td>
<td>165±25^a</td>
<td>n.a.</td>
<td>↑17-OHP, S and aldosterone in preterm sick compared to preterm healthy group</td>
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<tr>
<td></td>
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<td>sick (n = 9) and healthy (n = 13)</td>
<td></td>
<td>aldosterone, 17-OHP, 17-OH pregnenolone, S, 18-OH corticosterone, DHEA, DHEAS and androstenolone</td>
<td></td>
<td></td>
<td>n.a.</td>
<td>↑17-OHP, 17-OH pregnenolone and DHEAS in preterm compared to term group</td>
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<td>Term group: healthy (n = 16)</td>
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<td>Preterm healthy</td>
<td>190±29^a</td>
<td>n.a.</td>
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<td>Term</td>
<td>171±27^a</td>
<td>n.a.</td>
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<tr>
<td>Nykanen [101], 2010</td>
<td>67</td>
<td>23.6–33.1 weeks, sick Group 1:</td>
<td>0 and 4 days</td>
<td>Basal cortisol,</td>
<td></td>
<td>452 (61–2,704)^b</td>
<td>n.a.</td>
<td>↑17-OH pregnenolone and DHEAS but similar precursor ratios in group 1 compared to group 2</td>
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<tr>
<td></td>
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<td>&lt;28 weeks (n = 27) Group 2: ≥28 weeks (n = 40)</td>
<td></td>
<td>17-OHP, 17-OH pregnenolone, S and DHEAS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 days</td>
<td>277 (63–1,647)^b</td>
<td>n.a.</td>
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<td>4 days</td>
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<td><strong>ACTH test</strong></td>
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<tr>
<td>Thomas [42], 1986</td>
<td>52</td>
<td>Preterm group: 28–36 weeks,</td>
<td>3–4 days</td>
<td>Basal and ACTH-stimulated (36 μg/kg i.m.) cortisol and 17-OH-OP</td>
<td>Preterm sick</td>
<td>537±94^a</td>
<td>996±136^a</td>
<td>↑ peak 17-OHP in preterm sick compared to preterm healthy group</td>
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<td>sick (n = 24) and healthy (n = 15)</td>
<td></td>
<td></td>
<td>Preterm healthy</td>
<td>306±45^a</td>
<td>631±178^a</td>
<td>↑ basal 17-OHP in preterm compared to term group</td>
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<tr>
<td></td>
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<td>Term group: sick (n = 11)</td>
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<td></td>
<td>Term</td>
<td>372±157^a</td>
<td>645±101^a</td>
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</tr>
<tr>
<td>Hingre [28], 1994</td>
<td>25</td>
<td>&lt;30 weeks, sick</td>
<td>4 days</td>
<td>Basal and ACTH-stimulated (36 μg/kg) cortisol, 17-OH-OP, 17-OH pregnenolone and S</td>
<td>–</td>
<td>207±24^a</td>
<td>–</td>
<td>↑ cortisol precursors and S/cortisol ratio but similar cortisol compared to term reference</td>
</tr>
<tr>
<td>Kari [102], 1996</td>
<td>23</td>
<td>&lt;30 weeks, sick and healthy</td>
<td>13, 21 and 30</td>
<td>Basal cortisol, DHEAS, CBG and SHBG, and ACTH-stimulated (145 μg/m^2) cortisol</td>
<td>Dexamethasone, 13 days 125^a</td>
<td>607^a</td>
<td>–</td>
<td>–</td>
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<td></td>
<td></td>
<td>days</td>
<td></td>
<td></td>
<td>Placebo, 13 days</td>
<td>119^a</td>
<td>545^a</td>
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<td>Placebo, 21 days</td>
<td>176^a</td>
<td>817^a</td>
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<td></td>
<td>Placebo, 30 days</td>
<td>181^a</td>
<td>1,127^a</td>
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<tr>
<td>Korte [29], 1996</td>
<td>67</td>
<td>&lt;32 weeks, sick</td>
<td>2–3 days</td>
<td>Basal and ACTH-stimulated (0.1 or 0.2 μg/kg) cortisol, ACTH, DHEA, S and CBG</td>
<td>–</td>
<td>&lt;414 in 76% of cases</td>
<td>≥414 in 36% of cases</td>
<td>↑ S/cortisol ratio when basal cortisol &lt;414</td>
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<td>range: 0–24</td>
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<tr>
<td>Huysman [103], 2000</td>
<td>21</td>
<td>&lt;30 weeks, sick and healthy</td>
<td>4 days</td>
<td>Basal cortisol and 17-OH-OP, and ACTH-stimulated (0.5 μg cortisol)</td>
<td>–</td>
<td>277±144^f</td>
<td>753±250^f</td>
<td>↓ cortisol and ↑ 17-OHP/cortisol ratio in ventilated compared to nonventilated infants</td>
</tr>
</tbody>
</table>

Note: ACTH = adrenocorticotropic hormone; n.a. = not available; ↑ = increased; ^a = significance level; ^b = range; ^c = mean ± standard deviation; ^d = mean ± standard error of the mean; ^f = mean ± standard error.
**Table 1** (continued)

<table>
<thead>
<tr>
<th>First author [Ref., year]</th>
<th>n</th>
<th>Characteristics of participants</th>
<th>Age at assessment</th>
<th>Measurements Group</th>
<th>Cortisol (nmol/l)</th>
<th>ACTH (pmol/l)</th>
<th>Other findings</th>
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<td></td>
<td>Group 1</td>
<td>basal peak</td>
<td>basal peak</td>
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<tr>
<td>Bolt [34], 2002</td>
<td>24</td>
<td>&lt;33 weeks, healthy Group 1: &lt;30 weeks (n = 13) Group 2: 30–33 weeks (n = 11)</td>
<td>5–10 days</td>
<td>Basal cortisol, 17-OHP and E, and ACTH-stimulated (1 μg/kg) cortisol and 17-OHP</td>
<td>178±15a</td>
<td>515±33a</td>
<td>–</td>
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<td>Group 2</td>
<td>250±42a</td>
<td>733±89a</td>
<td>–</td>
</tr>
<tr>
<td>Kajantie [9], 2006</td>
<td>44</td>
<td>&lt;1,000 g, sick and healthy</td>
<td>1.6±1.1 days</td>
<td>Basal and ACTH-stimulated (0.06 μg/kg) cortisol</td>
<td>–</td>
<td>119 (55–300)e</td>
<td>261 (176–456)e</td>
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<td>CRH test</td>
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<td>–</td>
<td>275f</td>
<td>No rise in 3/10 cases</td>
</tr>
<tr>
<td>Rizvi [35], 1992</td>
<td>10</td>
<td>27.3±5.9 weeks, sick</td>
<td>7.5±9.4 days</td>
<td>Basal and CRH-stimulated (1 μg/kg) cortisol and ACTH</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td></td>
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<td></td>
<td>Study 1 (n = 13): basal and CRH-stimulated (1 μg/kg) cortisol and ACTH</td>
<td>350±115f</td>
<td>582±201f</td>
<td>6.9±2.1f</td>
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<td>Study 2 (n = 16): basal and CRH-stimulated (1 μg/kg vs. CRH 2 μg/kg vs. placebo) cortisol and ACTH</td>
<td>256±120f</td>
<td>509±167f</td>
<td>6.1±4.0f</td>
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<td>Study 2: CRH 1 μg/kg</td>
<td>330±15f</td>
<td>815±212f</td>
<td>4.5±1.5f</td>
</tr>
<tr>
<td>Ng [38], 1997</td>
<td>14</td>
<td>&lt;32 weeks, healthy</td>
<td>7 and 14 days</td>
<td>Basal and CRH-stimulated (1 μg/kg) cortisol and ACTH</td>
<td>–</td>
<td>396±67f</td>
<td>647±62f</td>
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<td></td>
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<td></td>
<td>Study 1</td>
<td>286f</td>
<td>513f</td>
<td>5.5f</td>
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<td></td>
<td>Study 2</td>
<td>233f</td>
<td>509f</td>
<td>7.1f</td>
</tr>
<tr>
<td>Ford [33], 1997</td>
<td>9</td>
<td>25.7±1.04 weeks, sick</td>
<td>19.9±8.04 days</td>
<td>Basal cortisol and ACTH; cortisol, ACTH and S after metyrapone 40 mg/kg; ACTH-stimulated (40 μg/kg) cortisol; CRH-stimulated (1 μg/kg) cortisol and ACTH</td>
<td>–</td>
<td>513±108f (&lt;414 in 2/9 cases)</td>
<td>684±448 after ACTH</td>
</tr>
</tbody>
</table>

17-OHP = 17-Hydroxyprogesterone; ACTH = adrenocorticotropin; B = corticosterone; CBG = cortisol-binding globulin; DOC = deoxycorticosterone; DHEA(S) = dehydroepiandrosterone (sulphate); E = cortisone; n.a. = not applicable; S = 11-deoxycortisol. a Mean ± SEM; b median (range); c mean; d mean ± SD; f geometric mean (interquartile range); g median; h data of infants without, or prior to, dexamethasone treatment; i the ACTH test was conducted 24 h after the CRH test; therefore, at the start of the ACTH test the basal cortisol level was already 604±131 nmol/l.
9 pmol/l or more was considered as adequate [37], although this was not a universal finding [38, 39]. Second, many studies showed that adrenal cortex enzymes were immature, and decreased 11β-hydroxylase activity was suggested to be the most important rate-limiting step [28, 29, 40–42]. Third, one study suggested that the interconversion between cortisol and cortisone favored cortisone with decreasing gestational age [43].

In infants born very preterm or with VLBW who experienced vasopressor-resistant hypotension, hydrocortisone or dexamethasone successfully enabled discontinuation of inotropics [44, 45]. Prophylactic glucocorticoids for prevention of hypotension were shown to be effective too in extremely preterm infants (i.e., <28 weeks of gestation) [46]. Similarly, extremely preterm infants exposed prenatally to synthetic glucocorticoids for fetal lung maturation had a lower likelihood of becoming hypotensive in the first days after birth [47]. In addition, in a study among preterm infants, proinsulin, insulin and C-peptide levels in cord blood remained elevated up to 48 h after the last steroid dose, in spite of a normal glucose concentration, suggestive of insulin resistance [48]. This might offer protection against neuroglycopenia. Consistent with these observations, the glucocorticoid bioactivity of a single treatment course of betamethasone was found to wear off 1–2 days after the last steroid dose [49].

From these data, it could be inferred that increased glucocorticoid bioactivity offers short-term benefits. Among infants with VLBW, the adrenocortical response to exogenous CRH rose significantly between postnatal days 7 and 14 [50]. The improvements were more marked for the group with hypotension necessitating inotropic treatment. The infants within it were also more premature and exhibited greater disease severity scores, suggesting that postnatal adversities could lead to a sustained increase in the response to CRH. It has not been tested whether such phenomena, which are probably adaptive in nature, persist beyond the early postnatal period and, subsequently, become maladaptive.

**Developmental Trajectories in Very Preterm Survivors beyond the Neonatal Phase: Footprints of Increased HPA Axis Activity?**

After an initial weight loss, birth weight is usually regained between the end of the 1st week and the 3rd week of life. Once birth weight is regained, the growth velocity increases to a level that approaches the intrauterine growth rate [51]. However, the rate of weight gain during hospital stay was shown to be slower in sick infants [51], which could be explained by suboptimal protein and calorie supplies for the level of illness.

After clinical improvement, catch-up growth in weight and length is initiated. At term age, while still being smaller and lighter, absolute fat mass and abdominal fat content were greater than in full-term newborns [52]. Although the major part of catch-up growth is completed by the age of 4 years, continuing catch-up growth in height, weight and body mass index was observed in late childhood and adolescence, albeit at a slower pace [51]. On average, in subjects born very preterm or with VLBW, final height was reduced by 0.5 SD compared to population-specific reference data [51]. Young adults born preterm or with VLBW, despite having a relatively normal body mass index, exhibited a lower lean mass, increased fat content and centralization of fat distribution [11, 14, 53, 54].

It is unlikely that the reduction in final height could be explained by an earlier onset or a more rapid progression of puberty. In cross-sectional studies of children aged 11–15 years, no differences in Tanner pubertal stages were demonstrated between boys and girls with VLBW and term-born children of the same age [55, 56]. Moreover, girls with VLBW reported a similar age at menarche as their term counterparts [55–57]. However, very preterm birth and/or VLBW were associated with an earlier pubertal growth spurt [57], a more advanced bone age at adolescence [55, 56] and adrenal hyperandrogenism in young adulthood [58, 59].

In very preterm survivors, antecedents of the metabolic syndrome were already present in childhood. Very preterm birth was associated with a relatively high blood pressure at 7.5 years of age, irrespective of the presence of nephrocalcinosis [60]. Furthermore, insulin sensitivity during an intravenous glucose tolerance test was reduced 4–10 years after very preterm birth. This was accompanied by a compensatory increase in acute insulin release [61].

Children born very preterm or with VLBW were found to display more internalizing problem behavior and attention problems as well as reduced scores on various cognitive tests [62]. Furthermore, imaging studies showed that very preterm birth and VLBW were associated with permanent reductions in, among other brain structures, hippocampal volume [63]. These patterns resemble those of term-born children who were exposed antenatally to higher maternal cortisol levels [64, 65].

Findings from studies addressing the long-term effect of prematurity on several aspects of HPA axis activity were...
contradictory (table 2). One study found that basal cortisol was higher in adults born preterm than in normal controls [58]. Another study found that this was already evident from the corrected age of 8 months for children born in the extremely preterm range [66]. Evidence for sex-specific effects was provided by Walker et al. [67], who compared adults born preterm, with or without IUGR, with normal controls. In women, plasma cortisol was not different, but the total urinary cortisol metabolite excretion was lower in the preterm non-IUGR group than in the other two groups, suggestive of impaired metabolic clearance. In contrast, no differences in cortisol parameters were observed in men. Yet another study found that ELBW was associated with higher excretion rates of adrenal steroid metabolites at age 10 years [68]. Two out of 4 studies that assessed the cortisol response to psychosocial stress found that preterm birth was associated with blunted rather than enhanced responses [69–72]. Preterm birth was also associated with a greater cortisol awakening response in childhood [69]. Furthermore, very preterm carriers of the 23K variant of the R23K polymorphism in the glucocorticoid receptor (GR) gene, which is associated with resistance to cortisol, were found to display complete catch-up growth before the age of 1 year, while in the noncarriers, the stature remained around the –0.5 SD line [74].

Table 2. Summary of studies that have assessed the HPA axis in children and adults born preterm

<table>
<thead>
<tr>
<th>First author [Ref.], year</th>
<th>n</th>
<th>Characteristics of participants</th>
<th>Age at assessment</th>
<th>Measurements</th>
<th>Main findings</th>
</tr>
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<tbody>
<tr>
<td>Szathmari [58], 2001</td>
<td>70</td>
<td>LBW: BW 900–2,500 g and GA ≤36 weeks; Controls: BW &gt;2,500 g and GA ≥38 weeks</td>
<td>~20 years</td>
<td>Blood specimen obtained at 7.30 h after overnight fasting for determination of cortisol and androgens</td>
<td>♂ Higher cortisol in LBW group ♀ Higher cortisol, DHEA, DHEAS and androstenedione in LBW group</td>
</tr>
<tr>
<td>Walker [67], 2002</td>
<td>52</td>
<td>Preterm AGA: BW &lt;2,000 g and &gt;10th centile; mean GA 32 weeks; Preterm IUGR: BW &lt;2,000 g and &lt;10th centile; mean GA 35 weeks; Controls: BW &gt;2,000 g; mean GA 39 weeks</td>
<td>22–25 years</td>
<td>Plasma cortisol at 9.00 h after overnight fasting, 24-hour urinary cortisol metabolite excretion</td>
<td>♂ No differences between groups ♀ Lower cortisol metabolite excretion in preterm AGA women and similar plasma cortisol, as compared to the other 2 groups</td>
</tr>
<tr>
<td>Wust [71], 2005</td>
<td>102</td>
<td>Male twins with GA 33–43 weeks and BW of 1,400–4,200 g</td>
<td>18.57±0.23 years</td>
<td>Salivary cortisol response during TSST</td>
<td>Higher cortisol response during TSST with decreasing BW and with increasing GA</td>
</tr>
<tr>
<td>Buske-Kirschbaum [69], 2007</td>
<td>36</td>
<td>Preterm: GA 26–36 weeks; Controls: GA 39–41 weeks</td>
<td>8–14 years</td>
<td>Salivary cortisol response during TSST, cortisol awakening response, diurnal salivary cortisol pattern</td>
<td>Higher cortisol after awakening in preterm group No differences in other outcomes between groups</td>
</tr>
<tr>
<td>Grunau [66], 2007</td>
<td>225</td>
<td>ELGA: GA 23–28 weeks; VLGA: GA 29–32 weeks; Controls: GA 37–42 weeks</td>
<td>3, 6, 8 and 18 months corrected age</td>
<td>Basal salivary cortisol</td>
<td>Higher cortisol at 8 and 18 months in ELGA group</td>
</tr>
<tr>
<td>Kaseva [70], 2014</td>
<td>94</td>
<td>VLBW: BW &lt;1,500 g and GA 24–36 weeks; Controls: GA 38–42 weeks</td>
<td>19–27 years</td>
<td>Salivary cortisol, and plasma ACTH, cortisol, glucose and insulin during TSST</td>
<td>Lower cortisol and insulin responses during TSST in VLBW group</td>
</tr>
<tr>
<td>De Graaf [73], 2014</td>
<td>79</td>
<td>NICU-treated: GA 30±3.1 weeks; Controls: GA 40±1.1 weeks</td>
<td>5 years</td>
<td>Diurnal salivary cortisol pattern</td>
<td>Higher cortisol over 24 h in NICU-treated group</td>
</tr>
<tr>
<td>Brummelte [72], 2015</td>
<td>129</td>
<td>Preterm: GA 24–32 weeks; Controls: GA 38–41 weeks</td>
<td>7 years</td>
<td>Salivary cortisol during cognitive tests, diurnal salivary cortisol pattern</td>
<td>Higher bedtime cortisol in preterm group No difference in cortisol during cognitive tests between groups</td>
</tr>
<tr>
<td>Gohlke [68], 2015</td>
<td>54</td>
<td>ELBW</td>
<td>8–11 years</td>
<td>24-hour urinary corticosteroid metabolite excretion</td>
<td>Higher corticosteroid metabolite excretion in ELBW group</td>
</tr>
</tbody>
</table>

AGA = Appropriate for gestational age; BW = birth weight; ELGA = extremely low gestational age; GA = gestational age; LBW = low birth weight; TSST = Trier Social Stress Test; VLGA = very low gestational age; ACTH = adrenocorticotropin.
In summary, these observations suggest that very preterm survivors show features of increased HPA axis activity that persist beyond the neonatal phase and extend into adulthood, although some studies were negative, and others, especially those that assessed the cortisol response to psychosocial stress, reported the opposite results. Signs of increased glucocorticoid bioactivity, such as an unfavorable body composition, raised blood pressure and insulin resistance, are already present in childhood [52, 60, 61]. Apparently, there is a large increment in the adrenal androgen production after an age-appropriate adrenarche, contributing to an earlier initiation of the pubertal growth spurt and advancement of bone maturation at adolescent age and, hence, earlier epiphyseal closure and shorter adult stature. The growth pattern of subjects born very preterm suggests that the growth-inhibiting actions of cortisol are outweighed by the anabolic effects of excess insulin and androgen levels.

**Exploring the Relation between Prematurity and Increased HPA Axis Activity in Later Life**

**Antenatal Glucocorticoid Therapy**

There is no doubt that administering glucocorticoids to mothers with impending preterm delivery is highly efficacious for the prevention of the respiratory distress syndrome and associated complications [75]. Although numerous animal studies in various species showed that administration of synthetic glucocorticoids throughout, or during part of, gestation causes permanent metabolic perturbations, neurobehavioral alterations and dysregulation of the HPA axis in offspring [2], it remains unclear whether a single treatment course of antenatal glucocorticoids could explain at least a part of the association between preterm birth and long-term outcome. First, associations between preterm birth and DM2 were also reported in middle-aged populations born before the introduction of antenatal glucocorticoids [13, 15]. Second, findings from studies investigating long-term outcome after antenatal glucocorticoid therapy were highly contradictory [76–81]. However, some of these studies were restricted to infants born very preterm or with VLBW [79–81], whereas others had followed all infants, regardless of whether they were born preterm or not [76–78].

**Postnatal Glucocorticoid Therapy**

Dexamethasone has been given to prevent or treat bronchopulmonary dysplasia (BPD). Compared to antenatal therapy, postnatal glucocorticoids are administered for a longer time (e.g., 1–3 weeks), resulting in substantially higher cumulative doses. Although dexamethasone during the first week of life was effective in the prevention of BPD, the risk of adverse outcomes, including poor growth and neurodevelopmental impairment, was increased, and therefore this therapy is not recommended [82]. However, dexamethasone could be considered after the 1st week of life to infants who cannot be weaned from the ventilator, provided that the dose and duration are kept to a minimum [83, 84]. Hydrocortisone may be as effective as dexamethasone in the prevention and treatment of BPD, and it has fewer side effects, though long-term follow-up data from randomized trials are lacking [83, 85]. Observational data, however, suggest that dexamethasone, when compared to hydrocortisone, for the facilitation of extubation was associated with an increased risk of adverse neurodevelopmental outcome and with reductions in cardiovascular and adrenal responses during a psychosocial stress test [86–88].

**Early Postnatal Care and Stress**

In animals, offspring subjected to maternal separation, or nonhandling, in early life exhibited dysregulation of the HPA axis, impaired cognitive capabilities, increased anxiety-like behavior and alterations in limbic structures [89]. Similarly, rat mothers that engaged in low amounts of licking and grooming with their pups had offspring that, as adults, were more responsive to stress [90]. This was associated with persistent alterations in DNA methylation and histone acetylation at the hippocampal GR 17 promoter, affecting nerve growth factor 1-A binding [90].

In humans, those who had experienced poor quality of parental care, such as neglect or emotional or physical maltreatment, early in childhood showed greater HPA axis activity and were at risk for mental illnesses, cardiovascular diseases and diabetes mellitus [91]. Furthermore, a study in hippocampal tissue from suicide victims showed that childhood abuse was associated with increased DNA methylation at the GR promoter and decreased expression of GR mRNA [92]. It is unknown whether these observations could be extrapolated to preterm babies, who are separated from their mothers after birth and, instead, are exposed to the stressful environment of the NICU. During admission to the NICU, exposure to stressors like invasive procedures, pain, interruption of sleep states and noise is common. Neonatal procedural pain-related stress after very preterm birth, however, has been associated with indices of cortisol production and HPA axis reactivity [72, 93, 94].
Neonatal Nutrition

There is increasing evidence to suggest that metabolic signals modify the HPA response to maternal separation [95]. In suckling mice, along with an increase in HPA axis activity, maternal separation elicited alterations in glucose, leptin and ghrelin concentrations [96]. Pharmacological manipulation of glucose or ghrelin levels attenuated the HPA response to maternal separation [96]. As adults, offspring subjected to prenatal or early postnatal malnutrition displayed greater HPA axis activity [95].

Current nutritional recommendations for preterm newborns advocate early introduction and rapid advancement of protein and energy [97]. Evidence from randomized trials and observational studies showed that strategies providing early, increased energy and protein support reduce nutritional deficits and improve neonatal growth and neurodevelopmental outcome [97]. In the intervention groups, amino acids and lipids were initiated early and rapidly increased to 3.5–4 g/kg per day. Nevertheless, in clinical practice, nutritional goals are rarely achieved and nutritional deficits ensue [98]. It is unknown whether this has life-long effects on the preterm human’s HPA axis.

Endogenous Glucocorticoid Sensitivity

In the challenging situation of very preterm birth, carriage of (sets of) genes that promote the response to vasoressors and/or the release of stored fuels may be beneficial. Indeed, there are some preliminary data to suggest that GR variants influencing cortisol sensitivity are related to the presence of several neonatal morbidities in babies with VLBW, albeit not consistently [99]. On the other hand, later in life, traits rendering increased glucocorticoid signaling were suggested to exacerbate the impact of antenatal glucocorticoids on the risk of developing adverse outcomes after very preterm birth, such as metabolic perturbations and poorer cognitive capabilities [81, 100].

Conclusions

Glucocorticoids, given their impact on blood pressure regulation and energy homeostasis, offer resilience to potentially life-threatening conditions after very preterm birth. Adaptation of HPA axis activity to the increased requirements of unintended postnatal life seems to be an attractive coping mechanism. It is suggested that once the burdens of neonatal life are no longer present, the HPA axis continues to be upregulated, leading to alterations in growth and developmental pathways, and, ultimately, to deleterious health consequences.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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Preterm Glucocorticoid Programming

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