The fetal and neonatal hypothalamic–pituitary–adrenal axis

P C Ng

The hypothalamus, pituitary, and adrenal glands are dynamic endocrine organs during fetal development.1–3 The adrenal glands, in particular, exhibit remarkable transformation in size, morphology, and function during the prenatal and neonatal periods.2 It is now recognised that normal development of the hypothalamic–pituitary–adrenal (HPA) axis is essential for: (1) the regulation of intrauterine homeostasis; and (2) the timely differentiation and maturation of vital organ systems including the lungs, liver, and central nervous system necessary for immediate neonatal survival after birth. In addition, acting together with the placenta, the HPA axis might indirectly control the normal timing of parturition in primates.1–3

The liberal use of exogenous antenatal and postnatal corticosteroids during pregnancy and early neonatal life have also raised concerns about potential adverse effects on the HPA axis and subsequent neurodevelopment.4 Thus, an understanding of the physiology and function of the HPA axis in intrauterine and extraterine life is important for neonatologists. This article aims to provide an overview on the physiology of the glucocorticoid axis and the effects that exogenous corticosteroids have on this system.

Basic physiology

Hormone activity in the HPA axis can be detected between eight and 12 weeks of gestation, early in fetal development.1–3 Corticotrophin releasing hormone (CRH) is produced from the fetal hypothalamus and the placenta during pregnancy. It is the primary secretagogue controlling pro-opiomelanocortin (POMC) mRNA expression and pituitary corticotroph secretion of adrenocorticotrophin (ACTH).1–3 CRH regulates the growth of pituitary corticotrophs, adrenocortical differentiation, and steroidogenic maturation of the fetal HPA axis.3 It is also a potent vasodilator of the fetoplacental circulation and can potentiate the function of local mediators and hormones, such as prostaglandins and oxytocin, in increasing myometrial contractility during labour.1 The progressive increase in the concentration of CRH in fetal and maternal circulations at late gestation suggests a pivotal role of placental CRH in modulating the timing of parturition (see below).1 ACTH is principally produced by the anterior pituitary corticotrophs and is the prime trophic hormone controlling fetal adrenocortical growth, differentiation, and steriodogenesis.1–3 ACTH acts via local mediators or growth factors, such as the vascular endothelial growth factor and epidermal growth factor, in synchronising fetal adrenocortical growth and angiogenesis.

The functional development of the fetal adrenal cortex is a highly complex process that involves the ontogenetical expression of specific steroidogenic enzymes in different zones and at different times in gestation.3 The fetal zone is the principal site of dehydroepiandrosterone sulphate (DHEA-S) production, whereas the definitive zone is the main site of mineralocorticoid synthesis. The transitional zone is functionally similar to the fetal zone early in development and is believed to be the site de novo cortisol production after 28 weeks of gestation.1 Cortisol is important in maintaining intrauterine homeostasis. It also influences the structural and functional development of a wide variety of fetal tissues, and is essential for the antepartum maturation of organ systems including the lungs, gastrointestinal tract, liver, and central nervous system, which are vital for neonatal survival.2

Regulation of the HPA axis

The regulation of the fetal HPA axis and its interaction with the placenta are illustrated in fig 1. The fetal hypothalamus responds to acute stressful situations such as arterial hypotension and haemorrhage by releasing CRH. CRH stimulates the production of ACTH from the fetal corticotrophs. The latter hormone enhances adrenal cortisol secretion, which in turn inhibits excessive CRH and ACTH release from the fetal hypothalamic–pituitary centres. ACTH also promotes DHEA-S secretion from the adrenocortical fetal zone, which provides substrates for oestrogen synthesis. Placental oestrogens indirectly influence the fetal HPA axis by facilitating the conversion of active cortisol into inactive cortisone, thereby reducing the concentration of cortisol in the fetus. This results in decreasing the negative feedback effects of cortisol on the fetal hypothalamic–pituitary centres and causes an increase in fetal POMC mRNA, ACTH, and adrenal cortisol production. An increase in fetal ACTH secretion further stimulates DHEA-S production.3 This positive feedback loop has been proposed...
Adaptation to extrauterine life
Because successful adaptation of newborns to extrauterine life relies on the exact timing of parturition and maturation of vital organ systems, the steroidogenic compartments of the fetal adrenal cortex must develop adequately and produce sufficient endogenous cortisol for perinatal survival towards the end of gestation. Despite the dramatic remodelling of the adrenal cortex that occurs immediately after birth, there is no evidence of clinical adrenocortical insufficiency in term infants during this crucial period. In contrast, ill and extremely premature infants form a unique group because of their potentially decreased ability to produce stress induced release of glucocorticoid. Recent studies suggest that some preterm very low birth weight infants, in particular those less than 1000 g, have inappropriately low serum cortisol concentrations but greatly raised concentrations of the cortisol precursors 11-deoxycortisol, 17-hydroxyprogesterone, and 17-hydroxypregnenolone when compared with term infants, indicating that the activity of some adrenal steroidogenic enzymes might be reduced as a result of adrenocortical immaturity. A large proportion of very low birth weight infants do not respond satisfactorily to stimulation by a physiological dose of ACTH (0.1 µg/kg). An inverse relation between gestational age and serum cortisol concentrations has also been described during the first 7 days of life in premature infants. In contrast to the above findings, Hanna and colleagues and Ng and colleagues have investigated the pituitary-adrenal function of very low birth weight infants using ovine and human CRH (1 µg/kg), respectively, and the results suggest that both ACTH and cortisol responses are adequate in most patients, with the configuration of the stimulation curves, the magnitude of responses, and the timing of the peak concentrations being comparable with those seen in the mature axis. Hence, it has been postulated that the relative inadequacy of cortisol production in some sick premature infants might be related to their inability to “recognise” stress or a failure of the hypothalamus to secrete CRH in stressful situations. Very low birth weight infants with low or suboptimal serum cortisol concentrations might have a higher risk of developing chronic lung disease and of requiring prolonged oxygen supplementation. Recent studies suggest that preterm human CRH stimulation appears to be intact but the adrenals fail to produce adequate cortisol to maintain normal blood pressure (PC Ng et al, unpublished data). This phenomenon, however, appears to be short lived and normal.
adrenal function returns within a month (PC Ng et al, unpublished data). The use of
narcotic drugs for pain or stress relief should also be carefully monitored, because these
agents might predispose to hypotension by lowering circulating concentrations of the
stress hormones.

The understanding of fetal and neonatal endocrine physiology has revolutionised the
management of preterm, very low birth weight infants in the past decade. This knowledge has
been clinically exploited by the use of antenatal and postnatal corticosteroids for advancing
lung maturation and treatment of chronic lung disease. The effects of exogenous cortico-
steroids on the HPA axis are discussed in the following sections.

Antenatal corticosteroids
The use of exogenous corticosteroids for
maternal or fetal indications during pregnancy
has raised concerns about their potential suppressive effects on the fetal HPA axis. Trans-
sient suppression of the pituitary–adrenal glands in preterm infants whose mothers received one to two doses of antenatal cortico-
steroids should recover by day 7 of life.12 18–20 Infants exposed to corticosteroids retain their
capability to respond to perinatal stress by pro-
ducing appropriate amounts of cortisol.20 In
addition, a recent study indicates that the pul-
satile nature of adrenal secretion is also undis-
turbed by recent maternal corticosteroid treat-
mant given within a seven day period before
delivery.21 However, the effect of multiple
courses of antenatal corticosteroid on the HPA
axis is less well defined. Although our initial
investigation using the human CRH stimula-
tion test suggested that the pituitary–adrenal
responsiveness of preterm infants at days 7 and
14 of postnatal life is unaffected when multiple
courses (mean, 7.2 doses) of antenatal dexam-
ethasone are administered to the mothers,12 our
latest evidence indicates that mild adrenal sup-
pression might be present in a small proportion
of preterm infants whose mothers received more than eight doses (mean, 11.6).22 A
significant negative correlation has also been
seen between poststimulation serum cortisol
concentrations and the cumulative antenatal
dexamethasone doses received by the
mothers.22 We can conclude from the current
evidence that a standard course (two doses) of
antenatal dexamethasone has no long lasting
suppressive effects on the pituitary–adrenal
function. Even multiple courses have relatively
little clinical or biochemical influence on the
HPA axis.12 22 The use of antenatal cortico-
steroids should not be withheld because of the
fear of HPA axis suppression.

Postnatal corticosteroids
Recent studies have shown that the HPA axis is
greatly suppressed after a three to six week
course of dexamethasone.23–26 Even a brief
period of exposure (five to seven days) might
result in severe suppression.27–29 However, a
repeatable three day pulsed course of dexam-
ethasone is associated with a lesser degree of
adrenal suppression when compared with a
continuous six week regimen.30 Studies using
ovine CRH, human CRH, and metyrapone
tests suggest that the hypothalamic–pituitary
centres are also suppressed by systemic
corticosteroids.24–26 Despite the high dose and
the prolonged course of treatment, most inves-
tigators have shown that in most infants HPA
axis function recovers within one to two
months after completion of the steroid
course.23–26 Although our results using the
human CRH stimulation test indicate that the
pituitary centre is able to recover earlier than the
adrenal glands,30 another study using the
metyrapone test suggests that, as a functional
unit, the hypothalamic–pituitary centres prob-
ably recover later than the adrenals.22 Steroid
replacement treatment might be desirable at
the time of stress in the immediate post-
treatment period, but seems unnecessary one
to two months after stopping systemic cortico-
steroid treatment.24 The effect of inhaled flutica-
sone propionate on the HPA axis has also
been assessed in a randomised controlled
study.31 A two week course of inhaled flutica-
sone propionate (1000 μg/day) produces mod-
erate severe pituitary–adrenal suppression in
very low birth weight infants.31 Inhaled cortico-
steroid is probably absorbed directly by the pulmonary vasculature and effec-
vantly circumvents the hepatic first pass metabolism, giving
rise to systemic side effects.32 Thus, we urge
vigilant surveillance in monitoring signs of
HPA axis insufficiency in severely ill infants
who have received postnatal systemic or high
dose inhaled corticosteroids, because the pitui-
tary and adrenal glands, although considered
to be biochemically active after one to two
months of stopping treatment, might have less
reserve compared with their pretreatment
state.33–35

Programming
Recent epidemiological evidence suggests that
stressful events experienced in fetal and early
neonatal life can produce enduring changes in
the structure and function of the neural
pathways, thereby resulting in alteration of the
programming process which predisposes to
specific diseases in later life.32–38 It has been
shown that early infant separation stress is
associated with an increase in adult psychopa-
thology, and a permanent rise in β endorphin
and cortisol in the circulation.39 Animal experi-
ments on rodents further indicate that perina-
tal manipulation of the HPA axis by exogenous
corticosteroids and stress might permanently
alter the development of central monoamine
neurones5 and reduce the CRH content in the
median eminence, which subsequently might
be associated with a decrease in stress induced
CRH release in adulthood.40 The administra-
tion of exogenous corticosteroids to pregnant
rats decreases the birth weight and raises the
blood pressure of their offspring in later life.41 A
relation between birth weight, blood pressure,
glucose tolerance, and HPA axis hormones is
also seen in humans. Fetuses and newborns
with estimated weight and birth weight less
than the 10th centile for gestational age have
increased umbilical venous ACTH and cortisol
concentrations when compared with larger fetuses and newborns of equivalent gestations. Cortisol values in adults were found to be highest in those who were lightest at birth. Low birth weight and raised serum cortisol concentrations are positively correlated with high blood pressure, but inversely related to glucose tolerance. Therefore, it has been postulated that perinatal stress and exposure to corticosteroids might induce long lasting changes in the HPA axis and alter individual's sensitivity to later environmental manipulations. Hence, the long term effects of antenatal and postnatal corticosteroids on the HPA axis and their potential to predispose to specific diseases in later life should be studied longitudinally, and carefully monitored.

Summary
Regulation of the fetal HPA axis is a highly complicated process and is under the control of positive and negative feedback circuits (fig 1), placental hormones, and local autocrine/paracrine mediators or growth factors. The primary aims of this complex system are to ensure appropriate coordination of tissue growth and differentiation, orderly maturation of vital organ systems, and ultimately to act together with the placenta to determine the exact timing of parturition most suitable for successful transition from intrauterine to extrauterine life. Undoubtedly, the understanding of basic fetal and neonatal neuroendocrine physiology and development has been clinically exploited and translated into new measures for revolutionising the management of preterm and newborn infants. Current evidence suggests that the antenatal and postnatal use of corticosteroids causes only transient suppression of the HPA axis, and endocrine function recovers within one week and four to eight weeks, respectively, in most infants after corticosteroid treatment has been stopped. However, because early treatment with exogenous corticosteroids might potentially influence the programming of the HPA axis, clinicians should monitor the long term effects of such exposure in treated cases.