Adrenocortical Function in Preterm Infants

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ABSTRACT

Adrenal hormones are essential for the timely differentiation and maturation of fetal organs and the regulation of intrauterine homeostasis. These hormones play complex roles during fetal life, and they are believed to provide the cellular communication that coordinates maternal-fetal interactions. Cortisol serves to modulate functional adaptations for extrauterine life in the perinatal period. Serum cortisol levels of preterm infants are similar to basal levels reported for healthy full-term neonates. However, a rise of cortisol production is absent during illness. Compared with a fetus of a similar gestational age, premature maturation of the hypothalamic-pituitary-adrenal (HPA) axis is suggested in preterm infants; however, the inappropriate cortisol value observed in severe illness is due to immaturity of 11 β -hydroxylase activity and an immature response of the brain to stress. Cardiovascular instability associated with adrenal insufficiency is more frequent than formerly reported, and replacing glucocorticoids in the treatment of refractory hypotension is effective without an increase in short term adverse consequences. However, the diagnostic criteria and optimal management have not yet been determined. Thus, further understanding of perinatal adrenal function will provide insight into the improved management of preterm infants.

Key Words: Preterm, Adrenal, Cortisol

INTRODUCTION

The adrenal cortex produces 3 categories of steroid hormone; glucocorticoids, mineralocorticoids, and adrenal androgens. Cortisol is a glucocorticoid, and it regulates a wide variety of physiologic processes from fetal to adult life. In the perinatal period, it serves to modulate functional adaptations for extrauterine life¹⁻⁴. The main functions of cortisol in the postnatal period are to regulate protein, carbohydrate, lipid, and nucleic acid metabolism; maintain vascular responsiveness to circulating vasoconstrictors and oppose the increase in capillary permeability during acute inflammation; regulate extracellular water by reducing movement of water into cells and promoting free water excretion; suppress the inflammatory response; and modulate central nervous system processing and behavior^{4,5}.

While the survival rate of preterm infants has improved over recent decades, preterm

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infants continue to present clinical manifestations associated with an abnormal cortisol axis. Infants with endocrine abnormalities are at increased risk of abnormal development and morbidity²⁻⁴).

This article briefly reviews the current understanding of the maturation of the adrenal gland, the roles of cortisol in the neonate's adaptation to extrauterine life, and the interpretation of clinical findings associated with adrenocortical function in pre-term infants.

FETAL ADRENAL CORTEX

The fetal adrenal gland exhibits a remarkable transformation in size, morphology, and function during the fetal and perinatal period^{1,6}. The fetal adrenal gland is composed of three functional zones: a fetal zone (FZ), a transitional zone, and an outer definitive zone. The FZ mainly produces androgenic precursors, the transitional zone contains enzymes for cortisol production, and

the definitive zone produces mineralocorticoids^{1,6}. Expression of steroidogenic enzymes from each zone during fetal life is different from those of postnatal life. Because the FZ has relatively high steroid sulfotransferase activity and low 3-beta hydroxysteroid dehydrogenase (3 β HSD) activity, the major steroid products of the fetal adrenal gland are dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS). There is a limited amount of cortisol and aldosterone produced⁶. There is also complementary activity between the enzymes involved in steroid formation and transformation between the placental and fetal compartments⁷ (Figure 1).

By 8 weeks gestation, the adrenal gland begins cortisol synthesis, which involves a transient expression of adrenal 3 β HSD^{1,6,8}. By 9 weeks gestation, the expression of 3 β HSD and the synthesis of cortisol decrease, and they are absent at 14 weeks gestation⁸. Before 23 weeks gestation, the human fetal adrenal cortex cannot produce cortisol de novo, and it normally does not do so until as late as 30 weeks gestation^{1,6,9}. The fetal cortisol production rate in the blood per unit body weight near term is similar to that

Figure 1. Steroid biosynthesis of fetus and preterm infant. The fetal zone of the human fetal adrenal cortex is capable of performing the reactions in the dotted line box. Since the fetal zone has relatively high steroid sulfotransferase activity, low 3 β HSD activity and low 11 β HSD, the major steroid products of the fetal adrenal gland are DHEA and DHEAS. In contrast, previous studies have shown no evidence of significant immaturity in adrenal 3 β HSD activity in preterm infants between 24-28 weeks gestation. Decreased activity of 11 β -hydroxylase explains relatively low cortisol levels in preterm infant. Abbreviations: DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; 3 β HSD, 3 β -hydroxysteroid dehydrogenase; 11 β HSD, 11 β -hydroxysteroid dehydrogenase; 17 β HSD, 17 β -hydroxysteroid dehydrogenase.

in the adult^{4,5}. Fetal cortisol is converted to cortisone through 11 β -hydroxysteroid dehydrogenase (11 β HSD) in fetal tissues, and levels of circulating cortisone in the fetus at mid-gestation are 4-fold to 5-fold higher than cortisol concentrations^{10,11}. The adrenocorticotropin (ACTH) feedback control system progressively matures during the second half of gestation and early neonatal period⁵. Maturation of the pituitary portal vascular system continues, and this maturation process extends to 30 to 35 weeks gestation⁵.

Steroid hormones produced by the fetal adrenal gland play key roles in the maintenance of pregnancy, intrauterine homeostasis, fetal maturation, and the initiation of parturition⁶.

In the term neonate, the adrenal gland undergoes rapid involution due to the rapid disappearance of the FZ. In contrast, the definitive zone, which contains an inner zona fasciculata and an outer zona glomerulosa, proliferates soon after birth^{1,6}. There is controversy about whether the timing of the fetal adrenal involution is determined by gestation or by birth⁶.

ROLE OF THE CORTISOL SURGE IN THE TRANSITION TO EXTRAUTERINE LIFE

After abrupt delivery, the neonate must initiate breathing and defend against hypothermia, hypoglycemia, and hypocalcemia as the placental supply of energy and nutrients are removed. The adrenal cortex rapidly responds to these changes.

Fetal cortisol levels in the human tend to be as low as 5-10 μ g/mL until approximately 30 weeks gestation. Cortisol levels progressively increase to approximately 20 μ g/mL by approximately 36 weeks gestation and increase further to approximately 45 μ g/mL at term. Cortisol further increases during labor to peak at high levels of approximately 200 μ g/mL several hours after a term delivery¹². This cortisol surge is mediated by a decreased rate of conversion of cortisol to cortisone and increased cortisol production by the fetal adrenal gland^{10,12}. The cortisol responses to preterm birth are also attenuated because of unresponsiveness and immaturity of the adrenal gland¹². In addition, cesarean section without labor at term blunts the postnatal rise in cortisol¹⁶.

The cortisol surge augments surfactant synthesis in lung tissue, increases reabsorption of liquid in the lungs, increases the methylation of norepinephrine to epinephrine, increases conversion of thyroxine (T4) to triiodothyronine (T3), facilitates ductus closure, induces maturation of several enzymes and transport pro-

cesses of the small intestine, and stimulates the maturation of hepatic enzymes⁵. Prenatal inflammation, such as that observed in chorioamnionitis, leads to adrenal stimulation, which results in increased cortisol secretion^{14,15}.

ADRENOCORTICAL FUNCTION OF PRETERM INFANTS

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is crucial to maintaining homeostasis in response to stress. Otherwise, the preterm infant would have a limited ability to maintain homeostasis after birth. Developmental immaturity and relative adrenal insufficiency due to illness may contribute to inadequate adrenocortical function. Adrenocortical function in preterm infants is closely related to the duration of gestation¹⁶. However, the cortisol production rate, assessed by urinary cortisol metabolites, of preterm infants of less than 30 weeks gestational age approaches the cortisol production rate of older children and adults. A rise in cortisol production is absent in preterm infants during clinical illness¹⁷. Cortisol levels are inappropriately low in some ill preterm infants, either due to the inability of the extremely premature brain to recognize the stress of the illness or because of inadequate hypothalamic secretion of corticotropin releasing hormone (CRH)¹⁸.

Although the human fetal adrenal cortex does not express the 3 β HSD enzyme before approximately 23 weeks gestation, previous studies have shown no evidence of significant immaturity in adrenal 3 β HSD activity in preterm infants between 24-28 weeks gestation^{19,20}. In contrast, decreased activity of 11 β -hydroxylase, which converts 11-deoxycortisol to cortisol, is prominent. Reduced activity of 11 β -hydroxylase, rather than that of 3 β HSD, is thought to explain the inappropriate production of cortisol in the preterm adrenal gland^{19,20} (Figure 1).

Blood concentrations of cortisol and other steroid hormones are not lower in preterm infants with late-onset adrenal insufficiency compared with control preterm infants²¹. These findings suggest that preterm infants might not have an absolute deficiency of cortisol production but rather a limited ability to synthesize sufficient cortisol for the corresponding degree of clinical stress.

EVALUATION OF ADRENOCORTICAL FUNCTION IN PRETERM INFANTS

The assessment of adrenocortical function in preterm infants is necessary, as immaturity of the HPA axis is related to clinical instability during acute stress. However, the best method of assessing adrenal function in preterm infants is still under debate.

The measurement of basal serum cortisol in preterm infants is not sufficient as a method for evaluating the function of the HPA axis. This is due to many influencing factors, such as the degree of stress and the effects of associated diseases. The real 'normal values' of serum cortisol are not available, as these are dependent upon both gestational age and postnatal age^{2,23}. While measuring serum cortisol levels in the early morning is a reliable method to evaluate the HPA axis in adults and children, it is not adequate in young infants, especially in preterm infants because the diurnal variation of cortisol is established during early infancy in term infants²⁴. Therefore, a dynamic test using ACTH or CRH is applied for the evaluation of preterm adrenocortical function.

A wide range of ACTH doses from 0.5-36 µg/kg have been applied for stimulating cortisol secretion in preterm infants²⁵. Different time-points for blood sampling are necessary to identify the peak cortisol level²⁶. The ACTH test only gives information about the secretory capacity of the adrenals and not pituitary or hypothalamic insufficiency. In this regard, the pituitary-adrenal system can be tested by the CRH test. However, the use of CRH is not the ideal method to test the integrity of the HPA system. The insulin-induced hypoglycemia test is suitable for evaluating the integrity of the HPA axis. However, because of the risk of brain damage induced by hypoglycemia, experience with this test is very limited²⁵.

Most of the cortisol produced in the adrenal glands is excreted in the urine as tetrahydrocortisol and tetrahydrocortisone conjugated with glucuronic acid^{5,25}. Unconjugated cortisol represents <1% of the adrenal secretion of this hormone in most situations^{5,25}. Therefore, the measurement of cortisol and its metabolite in 24-h urine specimens by chromatography and mass spectrometry is a reliable and noninvasive method of assessing cortisol production in preterm infants¹⁷. While such an approach primarily requires a reliable method of collecting 24-h urinary specimens, a challenging task with regard to babies, the urine collection is performed by using disposable pure cellulose

nappies from which the urine is recovered by hydraulic compression¹⁷.

Salivary cortisol measurement is a widely accepted alternative to the determination of cortisol levels in plasma or serum. The stress-free salivary collection for cortisol measurement has an advantage compared to plasma sampling because the adrenal cortex is responsive to the stress of venipuncture^{27,28}. Two methods of saliva collection have been used with preterm infants; using a commercial device to extract saliva from a small cotton ball and aspirating saliva using a small plastic tube²⁸. While some reports have suggested that salivary cortisol measurement is a reliable marker in critically ill subjects and preterm infants²⁹⁻³², its utility for preterm infants has not been confirmed³³. The ideal time to sample saliva after stress needs to be evaluated³¹.

ADRENAL INSUFFICIENCY IN PRETERM INFANTS

Activation of the HPA axis is crucial to maintaining homeostasis in response to stress. While there is no evidence of clinical adrenocortical insufficiency in term infants, ill and preterm infants may have a decreased ability to produce adequate amounts of glucocorticoids.

Systemic hypotension is a common complication in sick preterm infants. While the cause of hypotension in the preterm infant is multifactorial, multiple studies of extremely low birth weight infants have demonstrated hypotension that is refractory to volume expanders and vasopressors but responds to glucocorticoids^{34,35}. Recent studies have demonstrated low circulating levels of cortisol in preterm infants under stress, suggesting that the pathophysiology of systemic hypotension is associated with immaturity of the HPA axis^{17,21}.

Transient adrenocortical insufficiency of prematurity (TAP) is the term used to describe the clinical scenario in which preterm newborns in the immediate postnatal period have a normal or enhanced pituitary response but a transient inability of the adrenal glands to maintain cortisol homeostasis^{36,37}. TAP is frequently associated with systemic hypotension and results from an immature HPA axis and a reduced capability of the adrenal glands to produce cortisol secondary to a deficiency of intermediate enzymes, such as 11β-hydroxylase, in the synthesis pathway^{36,37}. TAP is typically transient, and adrenal function tends to return to normal by the end of the second week of life. Therefore,

glucocorticoid-responsive hypotension is not considered to be a common phenomenon in this population beyond the second week of life. However, preterm infants sometimes develop late-onset glucocorticoid-responsive circulatory collapse²¹⁾. The clinical picture of late-onset adrenal insufficiency in preterm infants (AIP) is not a result of an absolute deficiency of cortisol production; it may instead be due to a limited ability to synthesize sufficient cortisol for the degree of clinical stress²¹⁾. Clinical signs suggesting AIP include hypotension, oliguria, hyponatremia, lung edema, an increased demand for oxygen treatment without infection, hypovolemia, anemia, and the reopening of a patent ductus arteriosus²¹⁾.

There are no definitive diagnostic criteria for AIP. A presumptive diagnosis can be made if there is a clinical picture that is compatible with adrenal insufficiency, an inappropriately low serum cortisol level for the clinical scenario, and a rapid recovery from signs of adrenal insufficiency after cortisol replacement. A

serum cortisol level less than 15 µg/dL is one that is frequently used for the diagnosis of AIP. This level was determined following the proposed definition for relative adrenal insufficiency in critically ill adults and from the results of a study in critically ill term neonates that demonstrated improvement in hemodynamic parameters with hydrocortisone therapy in those patients with initial cortisol concentrations less than 15 µg/dL^{38,39)}. An increase in cortisol of less than 9 µg/dL in response to low dose ACTH stimulation (1 µg/kg of synthetic ACTH) is also used for the diagnosis of AIP. However, neither baseline cortisol <15 µg/dL nor Δ -cortisol <9 µg/dL were associated with the presence of relative adrenal insufficiency between the fifth and seventh days of life in preterm infants⁴⁰⁾. Some authors have recommended measuring the cortisol level in serum or saliva in response to a CRH test (1 µg/kg of hCRH) as a reliable method to evaluate the HPA axis in the preterm infant^{41,42)}.

Hydrocortisone is greatly preferred over dexamethasone for

Table 1. Summary of Published Studies on Adrenal Insufficiency in Preterm Infants

Study	n	GA (wks)	Postnatal age* (d)	Serum cortisol† (µg/dL)	Treatment
Bourchier and Weston, 1997 ⁵⁸⁾	HC: 21 Dopamine: 19	VLBW	<7	ND [‡]	HC 2.5 mg/kg, 4-6 hourly for 48 hours, followed by 1.25 mg/kg six hourly for 48 hours, and then 0.625 mg/kg for a further 48 hours before stopping treatment
Gaissmaier and Pohlandt, 1999 ⁵⁹⁾	17	28	2	ND	A single intravenous dose of dexamethasone 0.25 mg/kg
Seri et al, 2001 ⁶⁰⁾	21	26.9±3.9 [§]	11.3±13.1 [†]	ND	HC 2 mg/kg/d in 16 infants HC 3-6 mg/kg/day in 5 infants
Noori et al, 2006 ⁶¹⁾	24	26 (23-34) [§]	2 (1-24) [§]	ND	Dexamethasone 0.1 mg/kg followed by 0.05 mg/kg intravenously every 12 hours for 5 additional doses
Ng et al, 2006 ⁶²⁾	HC: 24 Placebo: 24	<32	11 (8-15) [§]	ND	HC 1 mg/kg every 8 hr for 5 days
Masumoto et al, 2008 ²¹⁾	11	26.8±2.4 [†]	13.1±4.1 [†]	6.6±4.5 [†]	HC 1-2 mg/kg/dose
Hochwald et al, 2010 ⁶³⁾	HC: 9 Placebo: 9	<28	<2	ND	HC 2 mg/kg for the first dose followed by three 6 hourly doses of 1 mg/kg and a further four doses of 0.5 mg/kg giving a cumulative dose of 7 mg/kg in 48 hr
Choi et al, 2011 ⁶⁴⁾	12	30.6±2.4 [†]	19±7 [†]	11.6±4.1 [†]	HC 4mg/kg/day for 1-2 days → 2 mg/kg/day for 1-2 days → 1 mg/kg/day for 1-2 days
Lee et al, 2011 ⁶⁵⁾	16	28±2 [†]	20±11 [†]	5.6±2.5 [†]	ND
Lee et al, 2013 ⁶⁶⁾	44	26.0±1.9 [†]	16.5 (5-158) [§]	ND	HC loading dose: 3-5 mg/kg/day → 3 mg/kg/day → 1 mg/kg/day
Shimokaze et al, 2015 ⁶⁷⁾	14	<29	21 (18-32) [§]	8.7 (1.5-34.8) [§]	HC 2-5 mg/kg → reduction of dosage (median 23 days)

Abbreviations: GA, gestational age; HC, hydrocortisone; VLBW, very low birth weight; ND, not described.

*Age of initiation of corticosteroid treatment.

†Serum cortisol level at the time of clinical manifestation of adrenal insufficiency.

‡Mean±standard deviation.

§Median (range).

|| ACTH stimulation tests were performed using Synacthen 35 µg/kg intravenously.

the treatment of AIP because it has less of an effect on the suppression of growth and has both glucocorticoid and mineralocorticoid effects. Various dosages and durations of hydrocortisone therapy have been used for the replacement of AIP (Table 1). According to a Cochrane review, hydrocortisone might be as effective as dopamine when used as a primary treatment for hypotension. However, the long term safety data on the use of hydrocortisone in this manner was unknown⁴³. In addition, glucocorticoids were effective in treating refractory hypotension in preterm infants without an increase in short term adverse consequences⁴³. Further studies to verify the diagnostic criteria, optimize treatment of AIP, and collect long term safety data are warranted.

SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an inherited metabolic disorder that affects 1 per 16,000 neonates^{44,45}. Mass screening of neonates for 21-hydroxylase deficiency identifies both male and female affected infants, prevents incorrect sex assignment, and decreases mortality and morbidity due to salt-wasting crisis. Most newborn screening programs measure 17-hydroxyprogesterone (17-OHP) from dried blood spots on filter paper. However, 17-OHP measurement in preterm infants has a high false-positive rate⁴⁶.

The mechanism underlying the high concentration of 17-OHP in preterm infants is not clearly understood because 21-hydroxylase is actively expressed in early mid-gestation and 3 β HSD is expressed in late mid-gestation¹. Possible explanations for the increased levels of 17-OHP in preterm infants include an increase in the conversion of cholesterol to pregnenolone due to increased ACTH from postnatal stress⁴⁷, a decrease in the conversion of 11-deoxycortisol to cortisol due to a delayed expression of 11 β -hydroxylase^{19,48}, and a decrease in the excretion of steroid metabolites from the kidney⁴⁵. Another probable explanation is that there is a crossed reaction in measuring 17-OHP with other steroid metabolites, such as 17-hydroxypregnenolone and its sulfated metabolites^{7,49}.

Specificity of newborn screening might be improved by using gestational age or birthweight to stratify subjects because 17-OHP levels are much better correlated with gestational age^{50,51}. However, there are no universally accepted standards for strati-

fying infants. Liquid chromatography-tandem mass spectrometry steroid profiling as a second-tier test on immunoassay results has also been introduced for reducing the burden of repeated tests for CAH screening^{52,53}. In addition, testing additional steroid profiles other than 17-OHP using liquid chromatography-tandem mass spectrometry is suggested to reduce the false-positive rate of CAH screening⁵⁴. One study, in which urinary steroid hormone metabolites were analyzed by gas chromatography-mass spectrometry, suggested that low 11 β -hydroxylase activity accounted for the high 17-OHP level in preterm infants and that 21-deoxycortisol or its urinary metabolite was more specific than 17-OHP for the diagnosis of classical CAH⁴⁸.

On the other hand, antenatal corticosteroid administration can interfere with screening programs for CAH because corticosteroids are known to suppress the HPA axis^{55,56}. Because betamethasone and dexamethasone are similar in their ability to cross the placenta and suppress the fetal pituitary-adrenal axis, the use of antenatal corticosteroids can increase the risk for decreasing 17-OHP levels in the blood spot, thus leading to false-negative results. The Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology have recommended that premature newborns need serial measurements of 17-OHP to differentiate false-positive and negative results from affected infants with CAH⁵⁰.

Although false-positive and false-negative rates of screening for CAH remain high in preterm infants, there is a low risk of missing a case of CAH that could lead to a salt-wasting crisis in the neonatal intensive care unit. Rescreening at regular intervals combined with careful monitoring of the clinical status in preterm infants with elevated 17-OHP levels is recommended⁵⁷.

CONCLUSION

Adrenal hormones play various roles in somatic development and maintenance of homeostasis throughout the fetal and neonatal periods. Serum cortisol levels of preterm infants are similar to basal levels reported for healthy full-term neonates. However, a rise of cortisol production is absent during illness. While premature maturation of the HPA axis is suggested in preterm infants, the inappropriate cortisol value despite severe illness is due to immaturity of 11 β -hydroxylase activity and an immature response of the brain to stress. Whereas abnormal

clinical findings associated with adrenal dysfunction are not rare in preterm infants, the diagnostic criteria and optimal management have not yet been determined. Further research is required to improve understanding of the pathophysiology and management of adrenal dysfunction in the preterm infant.

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