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COMMENTARY

Adrenal Insufficiency and Cardiac Dysfunction in the Preterm Infant

Commentary on the article by Yoder et al. on page 426

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Hypotension in the preterm infant is a significant precursor of major adverse outcomes, including mortality, intraventricular hemorrhage, and neurodevelopmental morbidity (1–4). While neonatologists may debate the exact definition of hypotension and the significance of any specific blood pressure (5), large numbers of very low birth weight infants receive symptomatic treatment with fluid boluses and inotropic support. In one study, for example, as many as 39% of VLBW infants received vasopressor support in the first 24 h after admission to the NICU (3). With the exception of patent ductus arteriosus, which may be the cause of hypotension in some infants, the etiology of this widespread phenomenon has remained unclear.

Over the past several years, investigators have begun to recognize a relationship between hypotension and adrenal insufficiency in preterm infants. Several reports have demonstrated that hypotension in this population responds to hydrocortisone treatment—including abstracts reporting cortisol insufficiency or "Addisonian crisis" (6, 7) and case series (8–10), as well as a randomized trial of hydrocortisone *versus* dopamine for treatment of hypotension (11). In addition, a large cohort study of premature infants found that those receiving inotropic support had significantly lower cortisol values than infants not receiving such support (12). This finding was surprising and noteworthy, since sick, stressed individuals should respond with activation of the hypothalamic-pituitary-adrenal axis, resulting in *increased,* rather than decreased cortisol concentrations (13).

The finding of inappropriately low cortisol concentrations in a subset of sick premature infants may be comparable to other critically ill populations, where the concept of a "relative" adrenal insufficiency has been described and linked to increased mortality (13–16). Patients with a relative adrenal insufficiency have cortisol values that might be considered normal for well individuals, but are inappropriately low for their degree of illness (13). The prevalence of this condition in patients admitted to intensive care units is not well characterized, but may be as high as 20% to 40% in patients with septic shock (14–16). Mechanisms postulated for this relative, or occult, adrenal insufficiency have included cytokine-related suppression of ACTH or cortisol synthesis (14), inadequate perfusion of the adrenal gland (14), or a limited adrenocortical reserve (13).

In the extremely premature infant, developmental immaturity might easily result in a limited adrenal reserve. Although the fetal adrenal cortex demonstrates remarkable hypertrophy during gestation, reaching organ weights that may exceed that of the adult, this hypertrophy is almost entirely due to enlargement of the fetal zone, which does not produce cortisol (17). As reviewed by Mesiano and Jaffe, studies suggest "that the human fetal adrenal cortex does not produce cortisol *de novo* from cholesterol until around week 30 of gestation" (17). Although the fetus may produce cortisol earlier in gestation using placental progesterone as a precursor (17), that substrate is no longer available to the newborn after birth, leaving the extremely preterm infant with a paucity of the enzymes required for *de novo* cortisol synthesis.

The concept of a relative adrenal insufficiency, or limited adrenal reserve in this population is consistent with published data showing that healthy premature infants can have very low cortisol concentrations without apparent ill effect (18), but that sick preterm infants do not show the increased cortisol values that would be considered appropriate in other populations (12, 13, 19, 20). In fact, one group of investigators reported that cortisol values were *inversely* proportional to the severity of illness in extremely preterm infants (21).

In this issue of the journal, Yoder and colleagues contribute to our understanding of the relationship of adrenal insufficiency to cardiovascular dysfunction in the extremely premature infant by examining that relationship in the extremely premature baboon (22). This group of investigators had previously developed a primate model of extreme prematurity (67% of gestation, approximating 26 wk human gestation) and discovered that "nearly two thirds. . .received inotropic and volume support to maintain blood pressure, urine output, and an acceptable acid-base status. Many were refractory to inotropic support, but, similar to very immature humans, responsive to replacement hydrocortisone therapy" (23).

Using this carefully controlled model of extreme prematurity, these investigators found that decreased urinary excretion

of free cortisol in the first day of life correlated with cardiovascular dysfunction and, further, that hydrocortisone replacement therapy improved cardiovascular function (22). They conclude that a substantial number of extremely premature baboons exhibit a transient adrenal insufficiency, which is manifested as cardiovascular dysfunction. Their conclusion is particularly convincing, first because the authors included measures of left ventricular function and systemic perfusion, rather than blood pressure values alone, and second, because they measured cumulative urinary free cortisol. Because urinary free cortisol excretion reflects both the active cortisol concentration in the plasma and total cortisol production over time, this measure provides a more accurate estimate of adrenal function than does an individual serum cortisol value (24).

A wide range of possible mechanisms for the relationship between adrenal insufficiency and cardiac dysfunction has been reviewed by these investigators and others (10, 22). Hydrocortisone replacement therapy could improve cardiac function by increasing calcium availability to muscle cells, reversing the down-regulation of adrenergic receptors, inhibiting nitric oxide synthase expression and/or prostacyclin production, decreasing the reuptake of norepinephrine, improving capillary integrity, or by other, as yet uncharacterized, mechanisms (10, 22).

This study adds convincing support to the growing evidence indicating the existence of a relative adrenal insufficiency of prematurity in extremely preterm infants. These authors link adrenal insufficiency to impaired cardiovascular function, and suggest that very brief hydrocortisone replacement therapy is sufficient for resolution (22); however, it may be that the urinary cortisol excretion pattern in the remainder of their experimental population still represents an insufficient response to acute illness. While 38% of the infant baboons received hydrocortisone, more than two thirds of the population required inotropic support for up to seven days to treat hypotension. Urinary free cortisol excretion rates in seriously ill infants and children have been reported to be 4–5 times normal values (24, 25), similar to the increase seen in the hydrocortisone-treated baboons.

Other features of this model support the hypothesis that relative adrenal insufficiency may be more prevalent and prolonged in the extremely premature primate, with additional adverse consequences. For example, the baboons in this experimental model have a very high incidence of patent ductus arteriosus and chronic lung disease (23). Lower cortisol values have been reported both in premature infants with PDA, and in those who subsequently develop bronchopulmonary dysplasia (26–30), and one study has found that hydrocortisone replacement therapy decreased the incidence of BPD (31).

While this baboon model is extremely valuable for its many parallels to the preterm human infant, it still has limitations, as the authors acknowledge. In particular, these baboons are delivered electively – rarely the case for human infants. Instead, over half of the human infants delivered at this gestational age show histologic evidence of inflammation in the placenta and/or umbilical cord (32, 33) – a situation which has been linked to increased pro-inflammatory cytokine concentrations in the newborn, and to adverse pulmonary and neurologic outcomes (34–36). One preliminary report has linked histologic chorioamnionitis with increased concentrations of IL-1β and IL-6 in cord blood and with significantly lower blood pressures in premature infants (37). Pro-inflammatory cytokines act as myocardial depressants (38), and additional cortisol may be necessary to counteract the effects of these cytokines (39).

Much work remains to be done to evaluate the prevalence, consequences, and treatment of relative adrenal insufficiency in the premature infant. Cortisol has a central role in maintaining physiologic stability; thus, adrenal insufficiency has been linked to adverse effects in many other organ systems; *e.g.* gastrointestinal dysfunction, increased inflammatory responses, and even neuronal apoptosis (39–41). Because high doses of glucocorticoid have been shown to produce myriad adverse effects (42), clinicians are appropriately reluctant to treat premature infants with low-dose hydrocortisone in the absence of results from large clinical trials. In addition, because the fetus is exposed to very low levels of cortisol *in utero*, many might suggest that these extremely premature infants should continue to be exposed to very low levels of cortisol. However, the sick premature infant may no longer have that option. Activation of the hypothalamic-pituitary-adrenal axis and increased cortisol concentrations may be essential to respond to the many stressors of extra-uterine existence.

The next logical step in this investigation is a randomized trial evaluating the interrelationship of cardiac and adrenal function in extremely preterm infants and the effect of hydrocortisone replacement therapy on cardiac function. Such a trial is underway (CH Cole, Tufts University School of Medicine, personal communication, 2001), as part of a multicenter trial evaluating the effect of hydrocortisone therapy on bronchopulmonary dysplasia. Continuing investigation of adrenal insufficiency, its consequences, and therapy in the well-controlled baboon model, combined with clinical trials in the chaotic world of the premature human infant, should bring us closer to a better understanding of the incidence and consequences of adrenal insufficiency in this population.

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SSRIs in Pregnancy –Are they safe?

Commentary on the articles by Oberlander *et al.* on page 443 and Morrison *et al.* on page 433

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An estimated 10% to 20% of women of reproductive age suffer from depression, often necessitating pharmacotherapy. During the last decade, there has been a dramatic shift in the treatment of patients with depression, with the selective serotonin reuptake inhibitors (SSRIs) largely replacing the tricyclic antidepressants. Typical of drug development, fluoxetine entered the market with reassuring animal reproductive studies but with no human experience. Because at least half of all pregnancies are unplanned, coupled with physicians and patients often being reluctant to discontinue effective drug therapy, postmarketing studies have gradually emerged on the safety of fluoxetine in pregnancy. Such studies have not shown evidence of morphologic or functional teratogenicity of fluoxetine (1–4).

Many women cannot discontinue their antidepressant therapy in pregnancy without a major negative impact on their well being. Einarson *et al.* have recently documented that "cold turkey" discontinuation of SSRIs and other psychotropic drugs in pregnancy can lead to substantial morbidity among women, including suicide ideation, hospitalization, and replacement of medications with alcohol (5). Hence, it is most important that the assessment of safety of medications in human pregnancy includes careful evaluation of the maternal and fetal risks of the untreated condition. A recently completed study of pregnancy outcome among children of women taking fluoxetine throughout pregnancy has failed to show any adverse effects on birth weight, preschool IQ, language development, or behavior. The study did find that the maternal level of depression (and not fluoxetine) is negatively associated with measures of child development (6).

This issue of Pediatric Research contains two studies from the University of British Columbia dedicated to the effects of SSRIs in pregnancy (7, 8). One study uses sheep as a model for physiologic changes associated with fluoxetine (7). The second study investigated neonatal pain response associated with SSRIs and benzodiazepines in pregnancy (8).