Altered adrenal steroid production in term infants having respiratory acidosis

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Prior studies have provided evidence for reduced fetal adrenal production of dehydroepiandrosterone sulfate and normal or increased production of cortisol in association with pregnancy complications believed to result in fetal stress. In the present study, we sought to determine the status of adrenal steroidogenesis in 36 term infants having respiratory acidosis and to compare acidotic infants to (i) non-acidotic infants matched for pregnancy complications, gestational age, and method and indications for delivery (control infants), and (ii) non-acidotic infants of non-complicated pregnancies who were also matched for gestational age and delivery method (normal infants). Umbilical cord serum levels of dehydroepiandrosterone sulfate were lowest in acidotic infants, intermediate in the condition matched control infants and highest in the non-acidotic infants of normal pregnancies. On the other hand, cortisol levels were highest in acidotic infants, intermediate in control infants and lowest in the normal infants. These data suggest that various pregnancy complications give rise to significant alterations in adrenal steroidogenesis (decreased dehydroepiandrosterone sulfate and increased cortisol). Intrauterine deterioration during labor with resultant respiratory acidosis has an additional effect on fetal adrenal function.

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Conditions such as maternal hypertensive disease (1) and congenital syphilis (2) have been shown to cause an unexpected, seemingly paradoxical effect on fetal adrenal steroidogenesis: umbilical cord serum levels of cortisol were normal or increased, but those of dehydroepiandrosterone sulfate (DHEAS) were subnormal in such infants. More over, the infants of women having severe pregnancy-induced hypertension had lower levels of DHEAS than did infants of women having mild pregnancy-induced hypertension (1). Whether these alterations in fetal adrenal function observed at the time of birth are representative of an acute intrapartum response rather than a chronic alteration in fetal adrenal function has been difficult to determine.

Many investigators consider respiratory acidosis in the newborn to be the result of a transient lack of oxygen due to intrapartum complications (3, 4). We reasoned, therefore, that newborns having respiratory acidosis might provide insights to the fetal adrenal response to acute intrapartum stress. To address this issue, we evaluated umbilical cord serum levels of DHEAS and cortisol in acidic newborns, non-acidotic newborns of women having the same pregnancy characteristics as those of the acidotic infants, and non-acidotic infants of women having no pregnancy complications.

Methods

Umbilical artery blood was obtained at delivery of term infants (37–43 weeks) for blood gas measurements (pH, HCO₃⁻, pCO₂, and pO₂). Umbilical cord venous blood also was collected for hormone analysis. Thirty-six neonates having respiratory acidosis (pH < 7.20, pCO₂ > 65 mmHg, and HCO₃⁻ > 17 mEq/l) were identified (pH 7.10–7.19, N = 26; pH 7.00–7.09, N = 8; pH < 7.00, N = 2) and matched one to one with a condition-matched control group of 36 non-acidotic infants (pH > 7.20) for gestational age (± 1 week), method of delivery, presence or absence of labor if delivered by cesarean section, date of delivery (generally within two weeks), and as closely as possible for complications during pregnancy. Sixteen pairs (44%) were delivered by cesarean section, and most of these (75%) occurred after the onset of labor. Epidural anesthesia and general anesthesia were employed in approximately equal proportions among the acidic and control pregnancies. As can be seen in Table 1, many pregnancies in both groups were complicated by one or more factors. Thus, we felt it would be informative also to compare such groups to normal newborns of women having no pregnancy complications. To this end, therefore, each of these pairs was also
Table 1. Complications in pregnancies with acidotic infants and their matched controls.

<table>
<thead>
<tr>
<th></th>
<th>HTN</th>
<th>DM</th>
<th>OLIGO</th>
<th>POST</th>
<th>IUGR</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidotic</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

HTN = chronic or pregnancy-induced hypertension; DM = non-gestational diabetes mellitus; OLIGO = oligohydramnios; POST = post-term; IUGR = growth retardation. Other includes gestational diabetes, sickle cell disease, Crohn's disease, syphilis, asthma and IV drug abuse.

Table 2. Blood gases in acidotic condition-matched control, and normal neonates.*

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>HCO₃⁻</th>
<th>pCO₂</th>
<th>pO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidotic (N = 36)</td>
<td>7.12 ± 0.011ᵇ</td>
<td>27.7 ± 0.4ᵇ</td>
<td>73.6 ± 0.9ᵇ</td>
<td>11.4 ± 0.9ᵇ</td>
</tr>
<tr>
<td>Control (N = 36)</td>
<td>7.28 ± 0.006ᵇ</td>
<td>22.5 ± 0.5ᵇ</td>
<td>51.2 ± 1.3ᵇ</td>
<td>20.5 ± 1.4ᵇ</td>
</tr>
<tr>
<td>Normal (N = 36)</td>
<td>7.29 ± 0.008ᵇ</td>
<td>22.8 ± 0.5ᵇ</td>
<td>50.9 ± 1.4ᵇ</td>
<td>16.4 ± 0.9ᵇ</td>
</tr>
</tbody>
</table>

* Data are presented as the mean ± SEM. pCO₂ and pO₂ are expressed in mmHg. Bicarbonate values are in mEq/l. Values with dissimilar superscripts differ significantly (p < 0.05).

matched for age of gestation (± 1 week) and mode of delivery with a non-acidotic infant of a completely normal pregnancy. A perfect match within each set of three infants was achieved for gestational age in 89% of the infant sets and for presence/absence of labor when delivered by cesarean section in 81% of infant groups.

Umbilical cord serum was stored at −20°C until utilized for quantification of cortisol and DHEAS by radioimmunoassay as described previously (5, 6). Hormone and blood gas data were evaluated by means of linear regression analysis and by repeated measures analysis of variance followed by Duncan's multiple range test.

Results

Umbilical cord blood gas measurements revealed expected similarities and differences among the three groups of neonates. As shown in Table 2 the acidotic group had significantly lower pO₂ values and higher pCO₂ values than control and normal neonates. Control and normal neonates exhibited similar values for pH, HCO₃⁻ and pCO₂, which also were within normal limits for vaginal term deliveries without complications (7). pO₂ values in the control group were higher than those in both the acidotic and the normal groups.

As shown in Fig. 1, the highest umbilical cord serum level of cortisol was in acidotic neonates, intermediate values occurred in the condition-matched controls, while normals had the lowest cortisol levels. In contrast, the DHEAS level and the DHEAS/cortisol ratio in the normal group were highest, and those of the acidotic group were the lowest. However, these indices of adrenal function in the acidotic group were not significantly different from those in the condition matched group.

An inverse correlation was noted between umbilical cord cortisol levels and pH (p < 0.01) whereas a positive correlation was observed between the DHEAS/cortisol ratio and pH (p < 0.01) among all 108 infants of our study. There was no statistically significant correlation between DHEAS and pH.

Discussion

The aims of the present study were twofold: (i) to determine whether intrauterine stress sufficient to cause acidosis in the new born also led to alterations in fetal adrenal steroidogenesis compared to that in pregnancy condition matched non-acidotic infants (control group); and (ii) to determine whether the adrenal function in acidotic infants differed from that of non-acidotic infants of women having no pregnancy complications. We found that acidotic infants had the highest serum levels of cortisol, the lowest levels of DHEAS and the lowest DHEAS/cortisol ratio among the three groups studied (p < 0.01 compared to non-acidotic infants of women having uncomplicated pregnancies). Acidotic infants also had significantly higher cortisol levels than did their condition-matched controls. In two prior studies, in which there was no matching for pregnancy complications, it also was noted that umbilical cord serum levels of cortisol are increased in acidotic infants (8, 9). Adrenal function, as judged by the serum DHEAS levels and by the DHEAS/cortisol ratio, in the acidotic infants was slightly, though not significantly different from that in the carefully selected group of control infants, who were matched on the basis of pregnancy complications in addition to gestational age and delivery method. Interestingly, this group of infants, like the acidotic infants, also had altered adrenal function when compared to the group of non-acidotic infants of women whose pregnancies were uncomplicated.

Our data suggest that function of the fetal adrenal is more sensitive to the stress resulting from pregnancy complications and/or altered placental blood-gas exchange than is acid base balance in the fetus. Consequently, adrenal function may be altered in utero (increased cortisol and decreased DHEAS production) in response to pregnancy complications without the concomitant occurrence of acidosis. Deterioration of the intrauterine environment during the intrapartum period in fetuses already stressed by maternal complications may lead to respiratory acidosis and a further perturbation of adrenal steroid secretion, particularly of cortisol.

The abnormal pattern of circulating steroids that we
find in acidic infants at birth is suggestive of possible stress-related changes in the steroid biosynthetic pathway in the fetal adrenal. Among the enzymatic activities of the fetal adrenal that are involved in the production of DHEAS and cortisol, those that could be involved in the response to stress that we have observed are $3\beta$-hydroxysteroid dehydrogenase, 17-hydroxylase and/or dehydroepiandrosterone sulfotransferase. An increase in $3\beta$-hydroxysteroid dehydrogenase activity could divert steroid substrate into the $\Delta^4$ pathway leading to cortisol at the expense of DHEAS. Reduction in the $17,20$ desmolase activity of 17-hydroxylase without alteration of the 17-hydroxylase activity could lead to diminished $C_19$ steroid formation without a reduction in cortisol production. Lastly, reduction in sulfurylation of dehydroepiandrosterone could similarly lead to reduced DHEAS production without any reduction in cortisol synthesis. As an alternative to changes in fetal adrenal steroidogenesis, it is conceivable that placental metabolism of DHEAS and/or cortisol is altered in maternal conditions that give rise to fetal stress and acidosis. An increase in placental sulfatase activity combined with a decrease in $11\beta$-hydroxysteroid dehydrogenase activity also could give rise to a decrease in umbilical cord serum levels of DHEAS and an increase in cortisol. Distinguishing among the above possible alterations in the feto-placental unit is a complex issue that, in the human, is not practical to address directly.

It is apparent that production of ACTH and other peptides derived from proopiomelanocortin such as $\beta$-endorphin and $\beta$-lipotropin is increased in stressed fetal (9, 10) and adult humans (11). Alterations in uteroplacental perfusion, hemorrhage, and experimental induction of acidosis in fetal lambs also have been shown to activate fetal ACTH and cortisol production (12–14). Since treatment of humans in vivo with ACTH is known to increase adrenal androgen production (15, 16), as also occurs in adrenal tissue exposed to ACTH in vitro (17), one might expect that DHEAS levels would also be increased in infants stressed in utero. Therefore, the finding of subnormal DHEAS levels in umbilical cord serum of acidic infants might be considered paradoxical. Nevertheless, it is becoming increasingly evident that the adrenal of the adult and fetal human responds to a variety of stressors by reduction in adrenal androgen production but activation of cortisol secretion (1, 2, 18–21). Therefore, it is possible that stress may also lead to increased production of substances that inhibit adrenal androgen production and/or impair production of a substance, such as the postulated adrenal androgen stimulating factor (22), that might ordinarily be required for maintaining adrenal androgen production at normal levels. The identity of such substances as well as the mechanisms responsible for alteration in their production in response to stress remain as important unanswered issues in human physiology.

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References

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