Placental 11β-Hydroxysteroid Dehydrogenase-2 and Fetal Cortisol/Cortisone Shuttle in Small Preterm Infants

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Glucocorticoids rate among the most controversial topics in today’s perinatology and neonatology. Many sick preterm infants exhibit signs of adrenal insufficiency, the etiology, diagnostic criteria, and optimal treatment of which are under debate. Moreover, most of these infants are exposed to pharmacological glucocorticoid doses both in utero and after birth. In face of this, surprisingly little is known about the physiological glucocorticoid exposure before early preterm birth. This exposure is highly variable and mainly regulated by the placental enzyme 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2), which converts excess cortisol (F) to inactive cortisone (E). Impaired activity of this enzyme is common in intrauterine growth restriction and preeclampsia, conditions frequently associated with early preterm birth. To identify clinical determinants associated with decreased placental 11β-HSD2 function, we studied 107 small preterm infants [mean birth weight, 1067 g (range, 395-2453 g); gestational age, 28.2 wk (range, 22.4–32.0 wk)] by determining their placental 11β-HSD2 activity rate (per milligram protein) and total activity (per placenta) as well as cord vein F and E concentrations. An E/(E + F) ratio expresses the overall balance of the F/E shuttle. There were positive correlations between relative birth weight and placental 11β-HSD2 activity rate ($r = 0.30$; $P = 0.002$) and total activity ($r = 0.56$; $P < 0.0001$) as well as E/(E + F) ratio ($r = 0.27$; $P = 0.01$) and E concentration ($r = 0.32$; $P = 0.003$). Infants with increased umbilical artery resistance had lower total placental 11β-HSD2 activity ($P = 0.02$), E/(E + F) ratio ($P = 0.04$), and E concentration ($P = 0.0002$). Gestational age was inversely associated with placental 11β-HSD2 activity rate ($r = -0.25$; $P = 0.009$). We conclude that, in small preterm infants, reduced placental 11β-HSD2 function is associated with low relative birth weight and severe fetal distress. Whether these conditions are associated with early postnatal adrenal insufficiency or long-term cardiovascular risk remains an important issue for further study. (J Clin Endocrinol Metab 88: 493–500, 2003)
Hospital, Helsinki, Finland, had their gestational age confirmed by ultrasound before 20 wk gestation. Infants from multiple pregnancies were included in the study only if they had clearly separate placentas. Infants of mothers receiving inhaled (n = 2) or systemic (n = 1) glucocorticoids, other than betamethasone to enhance fetal maturation, were excluded. The mean gestational age at birth was 28.4 wk (range, 22.4–32.0 wk), mean birth weight 1067 g (395–2453 g) and mean relative birth weight –1.26 sd (–4.90–3.40 sd). Table 1 shows the clinical data.

The infants and their placentas were weighed immediately after birth. Whenever possible, length and head circumference were also measured at birth, but in case an infant was too unstable to tolerate this, length and head measurements performed before 7 d of age were accepted because in sick preterm infants, skeletal (21) and head (22) growth during the first week are negligible. To describe intrauterine growth in units adjusted for gestational age, relative birth weight, length, and head circumference, expressed in sd units, were determined separately for both sexes with reference to current Finnish standards (23). Ponderal index was calculated as birth weight (kilograms)/[birth length (meters)] (3). Maternal hypertension during pregnancy was defined as systolic blood pressure of 140 mm Hg or more, diastolic blood pressure of 90 mm Hg or more, or a 30 mm Hg or more increase in systolic or 15 mm Hg or more increase in diastolic blood pressure. Preeclampsia was diagnosed when proteinuria of 0.3 g/d or more was present together with hypertension. Increased umbilical artery resistance index of 2 sd or more above mean for gestational age (24). Betamethasone (12 mg im twice at 12- or 24-h intervals, treatment repeated in 7 d) served as an antenatal glucocorticoid treatment when preterm birth was imminent. Treatment with betamethasone has been found to result in similar betamethasone concentrations in the maternal and fetal circulation (25). The diagnosis of gestational diabetes was based on oral glucose tolerance test, with venous plasma glucose exceeding 4.8 mmol/liter (baseline), 10.0 mmol/liter (1 h), or 8.7 mmol/liter (2 h).

The study protocol was approved by the Ethics Committee of the Department of Obstetrics and Gynecology, Helsinki University Central Hospital.

### Table 1. Clinical data

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean ± sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>107</td>
<td>28.2 ± 2.4</td>
</tr>
<tr>
<td>Birth measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (g)</td>
<td>107</td>
<td>1067 ± 414</td>
</tr>
<tr>
<td>Relative weight (sd)</td>
<td>107</td>
<td>–1.26 ± 1.53</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>75</td>
<td>36.4 ± 4.1</td>
</tr>
<tr>
<td>Relative length (sd)</td>
<td>75</td>
<td>–1.20 ± 2.18</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>72</td>
<td>25.6 ± 2.5</td>
</tr>
<tr>
<td>Relative head circumference (sd)</td>
<td>72</td>
<td>–1.06 ± 1.19</td>
</tr>
<tr>
<td>Placental weight (g)</td>
<td>100</td>
<td>271 ± 115</td>
</tr>
<tr>
<td>Placental 11β-HSD2 activity (pmol E/min/mg protein)</td>
<td>106</td>
<td>4.77 ± 2.13</td>
</tr>
<tr>
<td>Total placental 11β-HSD2 activity (μmol E/min)</td>
<td>99</td>
<td>1.29 ± 0.77</td>
</tr>
<tr>
<td>Cord vein F (nmol/liter)</td>
<td>89</td>
<td>48.1a</td>
</tr>
<tr>
<td>Cord vein E (nmol/liter)</td>
<td>89</td>
<td>120</td>
</tr>
<tr>
<td>Cord vein E / (E + F) ratio</td>
<td>89</td>
<td>0.70 ± 0.12</td>
</tr>
<tr>
<td>Male / female</td>
<td>56/51</td>
<td></td>
</tr>
<tr>
<td>Singleton / twin / triplet</td>
<td>90/14/3</td>
<td></td>
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<tr>
<td>Disorders of pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensionb</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Increased umbilical artery resistancec</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Diabetesd</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Cesarean sectione</td>
<td>69</td>
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</tr>
<tr>
<td>No. of antenatal betamethasone doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8</td>
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<tr>
<td>1</td>
<td>80</td>
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<tr>
<td>2</td>
<td>16</td>
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<tr>
<td>3</td>
<td>3</td>
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<tr>
<td>Time between last betamethasone dose and birth (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>24–72</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>&gt;72</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

a Geometric means.
b Excluding preeclampsia.
c Of infants with increased umbilical artery resistance, 21 came from pregnancies with preeclampsia and 9 from pregnancies with hypertension not fulfilling the criteria of preeclampsia.
d The number includes 3 infants of mothers with type 1 diabetes and 13 infants of mothers with gestational diabetes.
e The number includes eight cesarean sections during labor.
Cord vein F and E concentrations

Cord vein blood was drawn into EDTA tubes, with plasma separated immediately and stored at −20 C until analyzed. Plasma F concentrations were measured using a direct in-house method with antiseraum HPS631/1G (antisera, code SO20, Guildhay Ltd., Guildford, UK) and a cortisol-3CMO-histamine-[125-I] tracer as described by Moore et al. (28). Plasma E was extracted into chloroform, and the dried extracts were analyzed using a rabbit anticortisone antiseraum N-137 and a 21-acetyl cortisone-3CMO-histamine-[125-I] tracer (29). The cross-reactivity of E in the F assay was 1.2%, and of F in the E assay was less than 0.1%. Between-batch imprecision (percent coefficient of variation) for low-, medium-, and high-quality control samples ranged from 6.3% to 11.9% (F) and 6.1% to 10.0% (E).

Indicators of fetal F/E shuttle

Five different variables were used to illustrate different aspects of the fetal F/E shuttle. Placental 11β-HSD2 activity rate per unit placental weight was expressed as picomoles E per minute per milligram protein (1, 3). Total placental 11β-HSD2 activity was expressed as micromole E per min (1, 3). Cord vein F and E concentrations were as well used, and an E/(E + F) ratio was calculated to express the fraction of E of the total (E + F) pool (2). This ratio served as an indicator of the balance between 11β-HSD1 and 11β-HSD2 activity in those maternal and fetal tissues that contributed to the circulating concentrations.

Data analysis

Cord vein F and E concentrations were log transformed to normality. Partial correlation analyses including comparisons between two groups were adjusted for gestational age at birth, number of antenatal betamethasone doses, and time between the last betamethasone dose and birth. Adjustment for the time between last betamethasone dose and birth was performed by dividing the infants into three groups: 1) less than 24 h; 2) 24–72 h; and 3) over 72 h since last betamethasone or no betamethasone. Dummy variables were created for these groups to allow for possible nonlinear effects. The time limits were based on estimated proportion of glucocorticoid bioactivity caused by betamethasone during each period (30).

To assess which variables independently predict each index of placental 11β-HSD2 activity, multiple regression models were created by use of forward stepwise method starting from all variables with a significant univariate correlation with any of the indices. However, because of strong intercorrelations among different birth measurements, no other birth measurement than relative birth weight was included in the model.

Results

Table 1 presents the clinical characteristics of the study population as well as indicators of fetal F/E shuttle: placental 11β-HSD2 activity rate, total placental 11β-HSD2 activity, cord vein F and E concentrations, and the E/(E + F) ratio. All these indicators were similar in male and female infants and infants from singleton or multiple pregnancies. Placental 11β-HSD2 activity rate or total activity was not correlated with cord vein F or E concentrations or E/(E + F) ratio.

Disorders of pregnancy

Figure 1 shows that the 35 infants from pregnancies complicated by increased umbilical artery resistance had reduced total placental 11β-HSD2 activity, cord vein E/(E + F) ratio, and E concentration. These infants also had lower relative birth weight (−2.28 ± 0.23 vs. −0.75 ± 0.16, P < 0.0001) and smaller placentas (233 ± 24 vs. 292 ± 12 g, P = 0.001). However, there was no difference either in placental 11β-HSD2 activity rate calculated per milligram placental protein or in F concentration. Correspondingly, the 29 infants of mothers with preeclampsia had reduced total placental 11β-HSD2 activity (1.03 ± 0.12 vs. 1.40 ± 0.10 μmol E per minute, P = 0.01) and cord vein E concentration (119 ± 24 nmol/liter vs. 190 ± 22 nmol/liter, P = 0.03) but no difference in placental 11β-HSD2 activity rate (P = 0.5), cord vein E/(E + F) ratio, or F concentration. Comparison between the infants from all hypertensive (n = 49) and nonhypertensive pregnancies gave a similar result: lower total 11β-HSD2 activity (P = 0.001) and cord vein E concentration (P = 0.02) but no other difference.

Maternal diabetes was not associated with any index of fetal F/E shuttle. Infants born by cesarean section had lower placental 11β-HSD2 activity rate (P = 0.05) and total activity

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**Increased umbilical artery resistance**

Fig. 1. Boxplots (median, range, and interquartile values) comparing indicators of fetal F/E shuttle between small preterm infants from pregnancies complicated and those from pregnancies not complicated by increased umbilical artery resistance.
Gestational age and size at birth

Placental 11β-HSD2 activity rate, as assessed per milligram placental protein, decreased with increasing gestational age ($P = 0.009$; Fig. 2). This was, however, not accompanied by any association with total placental 11β-HSD2 activity or the cord vein E/(E + F) ratio (Table 2). Low relative birth weight (Fig. 2) was associated with reduced 11β-HSD2 activity rate ($P = 0.002$) and total activity ($P = 0.0001$) as well as lower cord vein E/(E + F) ratio ($P = 0.01$) and E concentration ($P = 0.003$). Further analysis of body proportions showed comparable associations with relative length at birth (Table 2). By contrast, relative head circumference and ponderal index at birth were associated only with total placental 11β-HSD2 activity ($P = 0.002$ and $P = 0.05$, respectively) but not with any other index of fetal F/E shuttle. Moreover, placental weight showed no correlation with 11β-HSD2 activity rate ($P = 0.9$) but, apart from the obvious association with total 11β-HSD2 activity, was also weakly associated with cord vein E/(E + F) ratio ($r = 0.19$; $P = 0.09$) and E concentration ($r = 0.25$; $P = 0.03$).

Antenatal glucocorticoid treatment

The total number of antenatal betamethasone doses given was inversely associated with cord vein F ($r = -0.38; P = 0.001$) and E ($r = -0.28; P = 0.009$) concentrations but not with E/(E + F) ratio or placental 11β-HSD2 activity rate or total activity. To assess the possible effect of the time between last glucocorticoid dose and birth, infants unexposed to betamethasone or with at least 72 h between last betamethasone dose and birth were selected to establish a reference group (30). Compared with this group, infants whose mothers had received betamethasone 24–72 h before birth had lower cord vein F ($P = 0.05$) and E ($P = 0.001$) concentrations and higher placental 11β-HSD2 activity rate ($P = 0.03$). By contrast, no

### Table 2. Correlations between indices of fetal F/E shuttle, birth measurements, and gestational age

<table>
<thead>
<tr>
<th></th>
<th>11β-HSD2 activity rate $r (P)$</th>
<th>11β-HSD2 activity (total) $r (P)$</th>
<th>Cord vein E/(E + F) $r (P)$</th>
<th>Cord vein F $r (P)$</th>
<th>Cord vein E $r (P)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>$-0.25 (0.009)$</td>
<td>$0.07 (0.5)$</td>
<td>$0.08 (0.5)$</td>
<td>$0.14 (0.2)$</td>
<td>$0.19 (0.07)$</td>
</tr>
<tr>
<td>Relative birth weight (SD)</td>
<td>$0.30 (0.002)$</td>
<td>$0.56 (-&lt;0.0001)$</td>
<td>$0.27 (0.01)$</td>
<td>$0.15 (0.2)$</td>
<td>$0.32 (0.003)$</td>
</tr>
<tr>
<td>Relative birth length (SD)</td>
<td>$0.19 (0.11)$</td>
<td>$0.42 (0.001)$</td>
<td>$0.41 (0.001)$</td>
<td>$0.06 (0.7)$</td>
<td>$0.34 (0.007)$</td>
</tr>
<tr>
<td>Relative head circumference (SD)</td>
<td>$0.13 (0.3)$</td>
<td>$0.38 (0.002)$</td>
<td>$0.21 (0.11)$</td>
<td>$0.05 (0.7)$</td>
<td>$0.20 (0.14)$</td>
</tr>
</tbody>
</table>

All correlations are adjusted for antenatal betamethasone treatment (number of treatments and time between last treatment and birth). Correlations with birth measurements are, in addition, adjusted for gestational age.

($P = 0.002$); these associations, however, became nonsignificant in a multiple regression model (see below).

### Gestation age and size at birth

Placental 11β-HSD2 activity rate, as assessed per milligram placental protein, decreased with increasing gestational age ($P = 0.009$; Fig. 2). This was, however, not accompanied by any association with total placental 11β-HSD2 activity or the cord vein E/(E + F) ratio (Table 2). Low relative birth weight (Fig. 2) was associated with reduced 11β-HSD2 activity rate ($P = 0.002$) and total activity ($P < 0.0001$) as well as lower cord vein E/(E + F) ratio ($P = 0.01$) and E concentration ($P = 0.003$). Further analysis of body proportions showed comparable associations with relative length at birth (Table 2). By contrast, relative head circumference and ponderal index at birth were associated only with total placental 11β-HSD2 activity ($P = 0.002$ and $P = 0.05$, respectively) but not with any other index of fetal F/E shuttle. Moreover, placental weight showed no correlation with 11β-HSD2 activity rate ($P = 0.9$) but, apart from the obvious association with total 11β-HSD2 activity, was also weakly associated with cord vein E/(E + F) ratio ($r = 0.19$; $P = 0.09$) and E concentration ($r = 0.25$; $P = 0.03$).
difference in any index of fetal F/E shuttle was seen in infants exposed to betamethasone less than 24 h before birth.

**Multiple regression models**

Multiple regression models shown in Table 3 demonstrate that placental 11β-HSD2 activity rate was independently associated with both relative birth weight and, inversely, with gestational age at birth, whereas low relative birth weight remained the sole factor to explain reduced total placental 11β-HSD2 activity. Antenatal betamethasone treatment was excluded from models explaining both placental 11β-HSD2 activity rate and total activity. However, treatment with betamethasone 24–72 h before delivery was, together with lower relative birth weight, associated with lower cord vein E/(E + F) ratio. It also predicted low E and F concentrations, which were also related to the total number of betamethasone doses given. Additional predictors for low E concentrations were low gestational age and impaired cord artery flow.

**Discussion**

In studying the clinical determinants of the fetal F/E shuttle at early preterm birth, we found low relative birth weight to be the strongest predictor of reduced F-to-E conversion, whether assessed by placental 11β-HSD2 activity or cord vein E/(E + F) ratio. Increased umbilical artery resistance, a sign of grave fetal distress frequently associated with e.g. severe preeclampsia, was similarly associated with reduced overall F-to-E conversion.

Despite the impressive capacity of placental 11β-HSD2, there are other regulators of the fetal F/E balance. 11β-HSD2 is expressed in a number of maternal and fetal tissues including the kidney and brain, in which this cytoplasmic enzyme regulates the access of F to mineralocorticoid or glucocorticoid receptors (7, 8). In several tissues, including adipose tissue, liver, and the fetal membranes but placenta only to a minor extent (31), the low-affinity enzyme 11β-HSD1 performs the inverse function: cytoplasmic conversion of E to F (9). To what extent different tissues contribute to F and E concentrations in fetal circulation is not known, but our finding of no correlation between placental 11β-HSD2 activity and the E and F concentrations or their ratio contrasts to a positive correlation observed in term infants (4). This suggests that between 22 and 32 wk gestation, the role of other fetal or maternal tissues in the fetal F/E interconversion is perhaps more significant than later during pregnancy.

Our finding of a clear correlation between relative birth weight and both placental 11β-HSD2 activity rate and cord vein E/(E + F) ratio is in agreement with similar findings in term or near-term pregnancies (1, 13) and studies reporting reduced 11β-HSD2 activity (4) and mRNA expression (6) in severe IUGR. The difference in placental 11β-HSD2 activity and expression between IUGR and normal pregnancies is actually accentuating with increasing gestational age (4, 6). Consequently, the solideity of the relationship with relative birth weight in the present study is perhaps surprising. It implies that even in small preterm infants, placental 11β-HSD2 activity and other determinants of the fetal F/E shuttle are significant contributors to size at birth. In an observa-
tional study, we could not assess whether small size at birth is a direct consequence of fetal glucocorticoid excess, and the possibility of an unknown cause affecting both placental 11β-HSD2 function and fetal growth through some other mechanism cannot be strictly excluded. However, fetal growth restriction is a plausible consequence of intrauterine glucocorticoid excess, and the finding that the strongest correlation of \(E/(E+F)\) ratio was seen with relative length at birth is consistent with the known effect of excess glucocorticoids in inhibiting longitudinal growth (32).

The magnitude of the association between relative birth weight and determinants of the fetal F/E shuttle can be deduced from the \(r^2\) values in Table 2. Consistent with the \(r^2\) values of the models in Table 3, the \(r\) values indicate that slightly less than 10% of the variation in relative birth weight is explained by variation in 11β-HSD2 activity rate or the \(E/(E+F)\) ratio. Correspondingly, about 30% of this variation is explained by variation in total placental 11β-HSD2 activity, which includes the effect of variation in placental size. Obviously, there are other contributors to fetal size, including the fetal and maternal genome and effects of nutrition and oxygen supply through other hormonal systems such as the insulin-IGF axis (33). An important question is whether different mechanisms of fetal growth retardation are operative in different disorders associated with prematurity and/or IUGR.

A major cause of prematurity is fetal distress severe enough to necessitate immediate delivery. Such fetal distress is commonly related to placental insufficiency associated with preeclampsia or nonpreeclamptic (i.e. without proteinuria) hypertension. These are overlapping conditions, many of the nonproteinuric hypertensive mothers representing an early stage of frank preeclampsia (34). Both are frequent causes of IUGR. Increased umbilical artery resistance is an end-stage feature of these and other disorders of impaired placental function and as such probably the most specific marker of severe fetal distress. Our finding of an association between increased umbilical artery resistance and reduced total placental 11β-HSD2 activity as well as cord vein \(E/(E+F)\) ratio and \(E\) concentration is consistent with the hypothesis that these conditions are associated with increased fetal glucocorticoid exposure. Moreover, we found reduced total placental 11β-HSD2 activity and \(E\) concentration in preeclampsia and hypertension, although contrasting to studies in term and near term-infants (13, 19), there was no difference in the 11β-HSD2 activity rate per se. It is therefore likely that between 22 and 32 wk gestation, the decreased overall F-to-E conversion in these conditions is attributable to smaller size of the placenta and possibly altered contribution of other fetal or maternal tissues, such as the maternal kidney (8). An intriguing explanation for the grossly reduced \(E\) concentrations could be an increased local conversion of \(E\) to \(F\) in fetal tissues. This would constitute a biologically meaningful way of increasing glucocorticoid effect during fetal distress despite relatively low \(F\) concentrations. However, there is so far little experimental evidence to substantiate this hypothesis.

We found placental 11β-HSD2 activity rate to decrease with increasing gestational age, although the effect on total placental activity was counterbalanced by increasing placentation size. This finding is at variance with others that show an increase in 11β-HSD2 activity (4) and mRNA expression (6) throughout pregnancy. However, Shams et al. (4) observed a similar negative correlation with gestational age within the IUGR group, possibly because of different pathophysiology of IUGR at different gestational ages. It is thus possible that the relatively large proportion of growth-restricted infants in our study may have contributed to this finding.

Antenatal glucocorticoid treatment is currently much debated. Despite its unequivocal benefit in reducing neonatal mortality and morbidity (20), administering repeated doses may instead increase mortality, reduce birth weight, and suppress the HPA axis (20, 35). We found the number of betamethasone treatments to be associated with a decrease in both \(F\) and \(E\) concentration in cord vein. Because maternal administration of betamethasone has been shown to result in similar betamethasone concentrations in maternal and fetal serum (25), this finding is likely to reflect both maternal and fetal HPA axis suppression. Otherwise the F/E shuttle appeared unaffected by the number of betamethasone doses. Whether betamethasone has any direct effect on placental 11β-HSD2 expression or function is poorly known, and our study with betamethasone administered on clinical indications was not designed to assess such direct effects. Instead, the significance of our findings lies in the notable capacity of 11β-HSD2 we found to exist also between 22 and 32 wk gestation and the large interindividual variation in this capacity as well as other determinants of the F/E shuttle. In fact, the side effects of betamethasone are observed already after relatively small doses, which result in a peak glucocorticoid activity of about 250 nmol/liter \(F\) equivalents and return to normal within 2–3 d (30). This underlines the potential importance of alterations in the fetal F/E shuttle, which could be expected to cause a similar or greater increase in overall glucocorticoid exposure.

The hypocortisolic fetal milieu created by placental 11β-HSD2 has been suggested to be crucial for the maturation of fetal HPA axis (1). With this in mind, the relationship we found between low relative birth weight and reduced placental 11β-HSD2 function in small preterm infants gives rise to putative long- and short-term health consequences.

A series of elegant studies in rodents link impaired placental 11β-HSD2 function with reduced birth weight and persistent alterations in tissue 11β-HSD2 and glucocorticoid receptor expression (16, 36), resulting in e.g. hypertension (16) and altered behavior (5). Although there are species differences, recent studies in humans point to a link between HPA axis function in adulthood, cardiovascular risk factors, and size at birth (17, 18). Although these associations are evident already within the range of normal term birth, small preterm infants have frequently suffered from grave IUGR and may receive large doses of glucocorticoids. They thus have much greater potential for adverse effects of early HPA axis programing, warranting thorough follow-up.

Many sick very low-birth-weight infants exhibit disproportionately low postnatal \(F\) concentrations, which are associated with e.g. subsequent chronic lung disease (37–40). This is a known phenomenon as well in adult intensive care, in which corticosteroid supplementation reduces the mor-
tality of hypocortisolemic patients (41). These observations have introduced the concept of early adrenal insufficiency, and in preliminary trials some infants indeed seem to benefit from low-dose early glucocorticoid replacement (42). However, at least high-dose glucocorticoids in small preterm infants are associated with major adverse effects including cerebral palsy (43) and cause concern because of possible lifelong HPA axis programming. It would therefore be crucial to identify infants with early adrenal insufficiency who might benefit from glucocorticoid replacement during the immediate postnatal period. Our finding of reduced 11β-HSD2 activity in infants with IUGR and/or severe fetal distress suggests that these infants constitute a susceptible group worth focusing on in prospective studies.

We conclude that infants born between 22 and 32 wk gestation exhibit large interindividual variation in placental 11β-HSD2 function and other determinants of the F/E shuttle. Within these infants, those born small for gestational age as well as those suffering from severe fetal distress have lower placental 11β-HSD2 function and reduced overall conversion of F to E. Possible health consequences to be addressed in further studies range from early postnatal adrenal insufficiency in small preterm infants to adverse HPA axis programing with increased adulthood cardiovascular risk.

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