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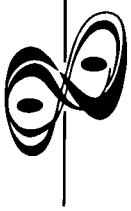

Fetal Adrenal Gland Maturation in Growth-Retarded Twin Pregnancies

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Twenty-two twin pregnancies each with one growth-retarded and one normal twin fetus were examined to determine the effects of fetal growth retardation on the maturation of the adrenal gland with respect to cortisol and dehydroepiandrosterone sulphate (DHEAS). The growth-retarded twin fetuses (IUGR) had lower umbilical arterial concentrations of DHEAS than their siblings (IUGR 5.25 ± 2.4; non-IUGR 6.51 ± 2.9 μmol/l; $p < 0.01$), whereas cortisol concentrations were not statistically different (no labor, IUGR 1,134 ± 751, non-IUGR 1,140 ± 958 μmol/l; labor IUGR 2,062 ± 929, non-IUGR 1,609 ± 469 μmol/l). These data suggest that while the definitive zone of the fetal adrenal is as well-developed as in non-growth-retarded twins, the fetal zone shows reduced secretory capacity of Δ^5-steroids. This supports the hypothesis that in growth retardation the adrenal gland shows features of increased maturation.

Key words: Growth retardation, Multiple pregnancy, Twins, Cortisol, Dehydroepiandrosterone sulphate, Fetal adrenal gland

INTRODUCTION

Poor intrauterine fetal growth may be associated with accelerated development of various organs; among these are the neurologic and pulmonary systems [1,2,5,14,16]. The maturation of some organs is dependent upon glucocorticoid-inducible enzymes [10], and some investigations have suggested that cortisol secretion is enhanced in growth-retarded fetuses [6,17]. Others, however, have reported normal or reduced adrenocortical activity in poorly grown neonates [9,13], and Naeye [11] described a significantly reduced adrenal mass in this group of fetuses.

We have proposed that twin pregnancy is a good model for the study of the effects of growth retardation and labor on the physiology of the fetus as age-matched, genetically similar siblings are available as controls [12]. The use of this model obviates the problems of transplacental passage of maternal hormones and the difficulty of obtaining suitably matched controls.

In this study we report on the maturation of the adrenal gland in growth-retarded twins with respect to dehydroepiandrosterone sulphate (DHEAS), the major secretory product

of the fetal zone of the adrenal cortex, and cortisol, which is produced in increasing quantities by the definitive (adult) zone with advancing gestation.

MATERIALS AND METHODS

Mothers with multiple pregnancies seen at the Twin Clinic who were booked for elective Caesarean section for standard obstetric indications gave informed consent to their participation in this study. Twenty-two patients gave birth to a growth-retarded fetus (defined as less than the 10th percentile for gestational age based on locally derived figures for singleton pregnancies [7]) together with a well-grown sibling. Ten women underwent surgery before the commencement of labor, while 12 were in early labor before Caesarean section could be performed. Blood obtained from the umbilical artery at the time of delivery was assayed for cortisol and DHEAS. Mean gestational age (derived from last menstrual period, early ultrasound, and assessment by physical and neurological scores) was 37 weeks and mean parity 2. The growth-retarded fetus was the presenting fetus in 9 of the 22 pregnancies.

The placenta was examined after each delivery to exclude macroscopic vascular anastomoses, and the twin transfusion syndrome was excluded by measurement of the packed cell volume. Definitive determination of zygosity was not performed.

Radioimmunoassay

Cortisol was measured by radioimmunoassay after separation of adrenal steroids by high-pressure liquid chromatography. The antibody (purchased from Clinical Assays, Travenol) cross-reacted with 11-desoxycortisol (5%), corticosterone (3%), and cortisone (3%); all other steroids cross-reacted less than 1%. DHEAS was measured by direct radioimmunoassay of the diluted plasma, using reagents purchased from Radioassay Systems Laboratories (Carson, CA). The only cross-reactions greater than 1% to the antibody were DHEA (100%), androstenedione (12.5%), and 16-hydroxy-DHEA (10%). Maternal plasma total estriol was measured on blood obtained at the time of delivery (Amersham, UK). Assay coefficients of variation were 8% (intra-assay) and 11% (interassay) for cortisol, 4% (intra-assay) and 12% (interassay) for DHEAS, and 4% (intra-assay) and 6% (interassay) for estriol.

Statistics

Significant differences ($P < 0.05$) between twin pairs were determined by the Wilcoxon test for nonparametric data. The Mann-Whitney test was used to assess differences between the groups.

RESULTS

Tables 1 and 2 show that there was significantly less DHEAS in the umbilical artery of the growth-retarded fetus, whereas cortisol concentrations were not significantly different between growth-retarded and normal groups. The expected increase in cortisol during labor was greater in those fetuses that were growth-retarded (82%) as compared to those that were not (41%), suggesting an enhanced response to the stress of labor. There was

TABLE 1. DHEAS Concentrations (μmol/l ± SD) in Umbilical Arterial Blood From Growth-Retarded (IUGR) and Non-Growth-Retarded (non-IUGR) Twin Neonates Before and During Labor

Labor group	n^a	IUGR	Non-IUGR	p
No labor	10	5.17 ± 2.4	6.52 ± 3.4	[b]
Labor	12	5.32 ± 2.5	6.49 ± 2.5	[b]
All patients	22	5.25 ± 2.4	6.51 ± 2.9	[c]

Abbreviations: DHEAS, dehydroepiandrosterone sulphate; SD, standard deviation.
[a]n = number in group.
[b]$0.02 < p < 0.05$.
[c]$0.025 > p < 0.01$.

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TABLE 2. Cortisol Concentrations (nmol/l ± SD) in Umbilical Arterial Blood From Growth-Retarded (IUGR) and Non-Growth-Retarded (non-IUGR) Twin Neonates Before and During Labor

Labor group	n^a	IUGR	Non-IUGR	p
No labor	7	113.4 ± 75.0	114.0 ± 95.7	NS
Labor	12	206.1 ± 92.7	160.9 ± 46.9	NS

Abbreviations: NS, not significant; SD, standard deviation.
[a]n = number in group.

TABLE 3. Total Estriol Concentrations (μmol/l ± SD) in Maternal Blood From Pregnancies With One Growth-Retarded Fetus (IUGR) and Pregnancies With Both Fetuses Well Grown (non-IUGR)

Labor group	IUGR	Non-IUGR
No labor	967 ± 199	810 ± 248
Labor	888 ± 409	900 ± 303

Abbreviations: SD, standard deviation.

no difference in maternal estriol concentrations between pregnancies with one growth-retarded baby and a similar group of twin pregnancies with fetuses that had grown normally (Table 3).

DISCUSSION

The adrenal cortex of the fetus in late gestation consists of two major subdivisions. The inner or fetal zone, being relatively deficient in the enzyme complex 3-β-hydroxy-$\Delta^4\Delta^5$-dehydrogenase (3BHSD), secretes mainly Δ^5-sulphated steroids, while the definitive or adult zone produces mainly 11-hydroxylated glucocorticoids. In normal fetal life, the relative inactivity of 3BHSD results in large amounts of secreted DHEAS as well as pregnenolone sulphate (Δ^5PS) and relatively small quantities of cortisol, which is required for fetal development [3,8,15].

With increasing maturity, however, the concentrations of DHEAS fall and those of cortisol rise, reflecting an enhanced contribution to adrenocortical secretion by the definitive zone of the cortex where 3BHSD activity is much increased.

The present study demonstrates that the fetal adrenal in growth retardation is able to secrete normal quantities of cortisol while producing reduced amounts of the Δ^5-steroid, DHEAS. This supports the observations made by Reynolds and Mirkin [13] who noted reduced Δ^5-3-β-hydroxysteroid metabolites and normal cortisol metabolites in the urine of growth-retarded singleton neonates. It also explains why estriol concentrations are lower in the cord blood of chronically stressed fetuses [4], because DHEAS is one of the precursors of steroids aromatized by the placenta. Although cortisol concentrations were not increased in the circulation of the growth-retarded twin, when compared to its sibling, the increase in plasma cortisol concentration during labor demonstrates that the secretory capacity of the adrenals of the growth-retarded fetus is as good, if not better, than that of the normal fetus. Because the twins were not subjected to the more stressful experience of vaginal delivery, it was not possible to assess the maximal secretory reserve of the adrenal gland.

Naeye [11] has shown that growth retardation leads to a greater decrease in the mass of the fetal cortex than of the definitive zone. As DHEAS is the principal secretory product of the fetal zone, a decrease in the mass of cells would be expected to lead to a diminished secretion of this Δ^5-steroid. An alternative explanation would be enhanced activity of 3BHSD due to removal of a postulated inhibitory hormone from the placenta [15]. Whatever the underlying mechanism, the pattern of adrenocortical secretion resembles a more mature stage of development in the growth-retarded fetus.

The present study has demonstrated that growth retardation in the twin fetus leads to an enhanced maturity of the fetal adrenal gland; it also reemphasizes the value of twin pregnancy as a model for the study of the effects of growth retardation on altered fetal growth and development.

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