Hypersecretion of FSH in Infant Boys and Girls Born Small for Gestational Age

LOURDES IBÁÑEZ, CARME VALLS, MARIA COLS, ANGELA FERRER, MARIA VICTORIA MARCOS, AND FRANCIS DE Zegher

Endocrinology Unit (L.I., A.F.), Hormonal Laboratory (C.V.), and Department of Pediatrics (M.C.), Hospital Sant Joan de Déu, University of Barcelona, 08890 Barcelona, Spain; Endocrinology Unit (M.V.M.), Consorci Hospitalari de Terrassa, 08227 Terrassa, Spain; and Department of Pediatrics (F.d.Z.), University of Leuven, B-3000 Leuven, Belgium

Prenatal growth restraint, as reflected in a low birthweight for gestational age, is a risk factor for postpubertal FSH hypersecretion and for reduced gonadal size. The ontogeny of the low-birthweight effect on the FSH-inhibin B feedback loop is unknown. Infancy is an episode of choice to study the possibility of an early low-birthweight effect on the FSH-inhibin B loop because this phase is characterized by high activity within the gonadal axis.

We assessed serum concentrations of FSH and inhibin B in 46 infants [26 girls and 20 boys; mean age, 4 months; range, 3–6 months; 17 appropriate for gestational age (AGA), 29 small for gestational age (SGA); mean birthweight, 3.2 kg for AGA vs. 2.3 kg for SGA], together with circulating levels of LH, E2, and free androgen index.

In SGA girls and boys, serum FSH levels were 2- and 4-fold higher (P < 0.001), respectively, than in AGA controls of the same gender (7.3 ± 0.9 vs. 3.8 ± 0.4 IU/ml and 2.9 ± 0.5 vs. 0.7 ± 0.2 IU/ml). Serum LH, inhibin B, and free androgen index/E2 concentrations were similar in AGA and SGA infants.

In conclusion, prenatal growth restraint was found to be followed by elevated serum FSH concentrations in infant girls and boys. SGA infants seem to need an augmented FSH drive to fulfill inhibin B requirements on the afferent side of the feedback loop. The late-endocrine correlates of early growth restraint are here-with extended to include the main axis of reproduction in both genders. It remains to be studied whether FSH hypersecretion in infancy is a marker of subsequent subfertility. (J Clin Endocrinol Metab 87: 1986–1988, 2002)

REDUCED PREGNATAL GROWTH has been associated with FSH hypersecretion and reduced gonadal size in adolescent boys and girls (1–3). Some low-birthweight effects on the endocrine system, e.g., those on adrenarche or insulin sensitivity, have been evidenced before onset of puberty (4–9), whereas other effects, e.g., those on lipidemia or systolic blood pressure, are not readily evidenced until after puberty (10, 11).

The time course of the low-birthweight effect on the FSH-inhibin B feedback loop is unknown. It is possible that this sensitive system, in which sex steroids are also involved, is already detectably affected in infancy, whereas the gonads may still present a morphometrically intact appearance (12). Infancy is an episode of choice to study the possibility of an early low-birthweight effect on the FSH-inhibin B loop, because this prepubertal phase is characterized by a high level of activity within the gonadal axis, in girls as well as in boys (13).

Accordingly, we have assessed the serum concentrations of FSH and inhibin B in appropriate- vs. small-for-gestational-age (AGA vs. SGA) boys and girls aged 3–6 months, the latter time window being located after the first phase of catch-up growth in SGA infants (14) and before the physiological decrease of activity in the gonadal axis (13).

Subjects and Methods

The study population consisted of 46 infants (postnatal age range, 3–6 months) in good general condition. Blood was sampled from this cohort at Barcelona Hospital, independent of this study and of birthweight, either for follow-up or screening purposes (including assessment of catch-up growth in SGA infants, blood group determination, assessment of nutritional status, and prevention or detection of anemia), before elective minor surgery (such as inguinal herniography or circumcision), or after recovery of intercurrent viral illness. Hormonal measurements for this study were performed either in a remaining aliquot of serum or in a small extra amount of serum (−2 ml) obtained for this purpose. The study protocol was approved by the Institutional Review Board of Barcelona Hospital. Before inclusion of infants, informed consent was obtained from the parents.

Inclusion criteria were: weight at term birth (37–41 wk) either AGA (between −1 and +1 so) or SGA (below −2 so), and postnatal age between 3 and 6 months.

Exclusion criteria were: evidence for syndromic, chromosomal or infectious etiology of low birthweight; hypothyroidism; urogenital tract abnormalities; systemic disease or acute illness; and persistent growth failure, defined as failure to increase length or weight by at least 1 so between birth and time of sampling.

Birthweight and gestational age data were obtained from hospital records and transformed into so scores, as described (6). Blood sampling for measurement of serum LH, FSH, inhibin B, SHBG, testosterone (T), and/or E2 was performed between 0900 and 1500 h. In boys, free androgen index [FAI; T (nmol/liter × 100/SHBG)], an index of free T (15), was calculated. After centrifugation, serum samples were kept frozen at −20°C until assay. Anthropometric data and endocrine results are expressed as mean ± SEM. A t test was used for statistical comparisons.

Serum LH and FSH were measured by immunochemiluminescence (IMULITE 2000, Diagnostic Products, Los Angeles, CA); the intra- and interassay coefficients of variation (CV) were 3.5 and 5.0% for LH and 4.6 and 6.3% for FSH, and the detection limit for both gonadotropins was 0.1 IU/ml. Serum E2 was measured by RIA using a commercially available double antibody kit (Diagnostic Products), with a detection limit of 1.4 pg/ml. The intra- and interassay CV were 5 and 4.9%, respectively. Inhibin B levels were assayed using the commercially available, double antibody enzyme-linked immunosorbent assay from Serotec (Oxford, UK); the lower limit of detection was 15.6 pg/ml; the intra- and inter-
TABLE 1. Birth data, age, and serum concentrations of hormones, related to gonadal function, in infant boys and girls who were born either AGA or SGA

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>AGA n = 7</td>
<td>SGA n = 13</td>
<td>AGA n = 10</td>
<td>SGA n = 16</td>
<td></td>
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<tr>
<td>Birthweight (g)</td>
<td>3.2 ± 0.05</td>
<td>2.3 ± 0.05a</td>
<td></td>
<td>3.2 ± 0.05</td>
<td>2.4 ± 0.05a</td>
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<tr>
<td>Gestational age (wk)</td>
<td>38 ± 0.3</td>
<td>39 ± 0.3</td>
<td></td>
<td>39 ± 0.4</td>
<td>39 ± 0.3</td>
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<tr>
<td>Postnatal age (months)</td>
<td>4.7 ± 0.6</td>
<td>4.0 ± 0.3</td>
<td></td>
<td>4.4 ± 0.4</td>
<td>3.9 ± 0.3</td>
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<tr>
<td>LH (IU/ml)</td>
<td>1.5 ± 0.6</td>
<td>1.3 ± 0.2</td>
<td></td>
<td>0.2 ± 0.1</td>
<td>0.3 ± 0.1</td>
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<tr>
<td>FSH (IU/ml)</td>
<td>0.7 ± 0.2</td>
<td>2.9 ± 0.5a</td>
<td></td>
<td>3.8 ± 0.4</td>
<td>7.3 ± 0.9a</td>
<td></td>
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<tr>
<td>Inhibin B (pg/ml)</td>
<td>280 ± 23</td>
<td>332 ± 34</td>
<td></td>
<td>58 ± 6</td>
<td>65 ± 6</td>
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<tr>
<td>FAI</td>
<td>2.0 ± 0.7</td>
<td>2.8 ± 0.5</td>
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<tr>
<td>E2 (pg/ml)</td>
<td></td>
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<td>91 ± 33</td>
<td>73 ± 21</td>
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</tr>
</tbody>
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Values are mean ± SEM.

a P < 0.001 vs. AGA.

Results

Gestational age in AGA and SGA cohorts was similar (38.3 ± 0.3 vs. 39.0 ± 0.2 wk), whereas birthweight was, by definition, different (3.2 ± 0.1 vs. 2.3 ± 0.1 kg). At time of study, length and weight of AGA vs. SGA infants were 62.5 ± 2.6 vs. 59.4 ± 4.1 cm (P < 0.01) and 6.6 ± 0.8 vs. 5.4 ± 0.1 kg (P < 0.0001).

Table 1 summarizes birth and age data and endocrine results. Figure 1 shows that FSH was elevated in SGA infants compared with AGA controls.

Serum LH, inhibin B, FAI, and E2 levels were similar in AGA and SGA infants.

Discussion

A reduction of prenatal growth was found to be associated with a reset of the FSH-inhibin feedback loop in infant girls and boys. In SGA infants, gonads seem to need an augmented FSH drive to fulfill the inhibin B requirements on the afferent side of the loop. Post-SGA hypersecretion of FSH is relatively more pronounced in infant boys than girls, possibly because the physiological feedback level of inhibin B is higher in boys (12, 17), and because the interindividual variation in the relationship between circulating FSH and inhibin B is smaller in boys than in girls (13).

The mechanisms governing post-SGA hypersecretion of FSH in both genders are currently unknown. A unifying hypothesis would be that poor fetal growth conditions result in reduced fractions of granulosa and Sertoli cells within the gonads, just as they can interfere with differentiation of the external genitalia (18, 19). In the female fetus, prenatal growth restraint has been associated with a reduced fraction of primordial follicles (20). The present findings may ultimately be of relevance for reproductive medicine because the time span of female fertility seems to be codetermined by the original number of primordial follicles and by the rate of apoptosis (21), and because there is experimental evidence indicating that adult testicular size and sperm output relate to the number of Sertoli cells generated perinatally (22).

Regardless of the mechanisms that will prove to be involved, the late-endocrine correlates of early growth restraint are herewith extended to include the main axis of reproductive function in both genders. It remains to be verified whether FSH hypersecretion in infancy is predictive of male or female subfertility in adulthood. Prenatal growth and infantile FSH secretion may become novel components to be integrated into the assessment of human subfertility.

Acknowledgments

We thank Consol Sánchez for facilitating the collection of the study samples, Montserrat Gallart for hormone measurements, and Inge Laleeuwe for editorial assistance.

References


22. Orth JM, Gunsalus GL, Lamperti AA 1988 Evidence from Sertoli cell-depleted rats indicates that spermatid number in adult depends on numbers of Sertoli cells produced perinatally. Endocrinology 122:787–794