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Precocious Pubarche, Hyperinsulinism, and Ovarian Hyperandrogenism in Girls: Relation to Reduced Fetal Growth

LOURDES IBÁÑEZ, NEUS POTAU, INGE FRANCOIS, AND FRANCIS DE ZEGHER

Adolescent and Endocrine Unit (L.I.) and Hormonal Laboratory (N.P.), Hospital Universitari Materno-Infantil Vall d'Hebron, Barcelona, Spain; and the Department of Pediatrics, University of Leuven (I.F., F.d.Z.), Leuven, Belgium

ABSTRACT

Pronounced adrenarche with precocious pubarche (PP) in girls has been associated with hyperinsulinism and subsequent functional ovarian hyperandrogenism (FOH). Recently, pronounced adrenarche and insulin resistance have each been related to low birth weight. We have now tested the hypothesis that the frequent concurrence of PP with pronounced adrenarche, FOH, and hyperinsulinemia in girls may be secondary to separate relationships between these conditions and low birth weight.

A total of 185 girls (aged 5–18 yr) without endocrinopathy or with PP and pronounced adrenarche with or without FOH were studied; mean serum insulin (MSI) concentrations were determined after a standardized oral glucose tolerance test. Birth weight SD scores [mean (SEM)] of control girls (0.38 ± 0.08; n = 83) were higher ($P < 0.0001$) than those of PP girls (−0.81 ± 0.13; n = 102). Among postmenarcheal PP girls, birth weight SD scores of girls without FOH (−0.25 ± 0.19; n = 25) were higher ($P < 0.0001$) than those in girls with FOH (−1.51 ± 0.28; n = 23). In pubertal girls (n = 145), MSI levels correlated negatively with birth weight SD scores (r = −0.48; $P < 0.05$), independently of PP. MSI levels in girls with birth weight below 1 SD (93 ± 9 mU/L; n = 33) were higher ($P < 0.0001$) than those in girls with birth weight between −1 and +1 SD (52 ± 2 mU/L; n = 94), whereas glycemia profiles were comparable.

Integration of the aforementioned data suggests that there may be a sequence in the associations between reduced fetal growth and components of the postnatal endocrine system; minor fetal growth reduction appears to be associated with amplified adrenarche, whereas more pronounced prenatal growth restriction seem to precede FOH and hyperinsulinemia during adolescence.

In conclusion, these findings corroborate the hypothesis that the frequent concurrence of PP (with pronounced adrenarche), FOH, and hyperinsulinemia in girls may result from a common early origin (low birth weight serving as a marker), rather than from a direct interrelationship later in life. (*J Clin Endocrinol Metab* **83:** 3558–3562, 1998)

PRONOUNCED adrenarche with precocious pubarche (PP) in girls has been associated with hyperinsulinism and subsequent functional ovarian hyperandrogenism (FOH) (1–3); the latter is characterized by an abnormal ovarian 17-hydroxyprogesterone (17-OHP) response to challenge with a GnRH analog regardless of whether elevated serum LH levels or polycystic ovaries are present (4, 5). Recently, pronounced adrenarche (6) and insulin resistance in children (7) as well as male gonadal dysfunction (8) have each been separately related to reduced fetal growth.

We have now tested the hypothesis that the frequent concurrence of PP with pronounced adrenarche, hyperinsulinemia, and FOH in girls may be secondary to separate relations between these three conditions and reduced fetal growth, as judged by low birth weight.

Subjects and Methods

Subjects

One-hundred and two PP girls (age range, 5–18 yr) and 83 Tanner stage- and bone age-matched controls (9, 10) (age range, 6–16.6 yr) were studied. Controls were selected from short normal children (heights between the 10th and 25th percentiles) and other children being seen by other unrelated pediatric subspecialties. Subjects were divided into 4 groups according to Tanner stage of breast development (9): prepubertal (B1), early pubertal (B2), midpubertal (B3), and postmenarcheal (B5). Body mass indexes (BMI) were normal in all subjects (11) and did not differ significantly between patients and controls within the same pubertal stage. In all patients, PP was secondary to premature adrenarche; namely, they presented with elevated androstenedione (Δ^4-A) and/or dehydroepiandrosterone sulfate (DHEAS) levels at PP diagnosis (12–14).

Twenty-three of the 48 postmenarcheal girls were classified as having FOH, *i.e.* they presented with oligomenorrhea (defined as menstrual cycles of >45-day duration) or amenorrhea and hirsutism (indicated as a score of 8 or more on the Ferriman-Gallwey scale) (15) in the face of elevated baseline serum Δ^4-A, total testosterone (T), and/or free androgen index [FAI; T × 100/sex hormone-binding globulin (SHBG)] and an elevated ovarian 17-OHP response to challenge with the GnRH analog leuprolide acetate (>160 ng/dL) (1, 16).

None of the subjects had acanthosis nigricans, thyroid dysfunction, Cushing's syndrome, hyperprolactinemia, a family or personal history of diabetes mellitus, or late-onset congenital adrenal hyperplasia (17, 18).

Postmenarcheal girls were studied in the follicular phase (days 3–8) of the menstrual cycle. The protocol was approved by the institutional review committee at Barcelona Hospital. Informed consent from patients or their parents was obtained as well as assent from minors. The baseline clinical characteristics of all groups are described in Table 1, and the prestudy hormonal variables for postmenarcheal patients are depicted in Table 2.

Methods

After 3 days of a high carbohydrate diet (300 g/day) and an overnight fast, a standard 1.75 g/kg BW (maximum, 75 g) 2-h oral glucose tolerance

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Address all correspondence and requests for reprints to: Lourdes Ibáñez, M.D., Ph.D., Adolescent and Endocrine Unit, Hospital Universitari Materno-Infantil Vall d'Hebron, P° Vall d'Hebron 119–129, 08035 Barcelona, Spain. E-mail: lourdes.ibanez@deinfo.es.

TABLE 1. Clinical characteristics of patients and controls

Tanner breast stage	CA (yr)	Ht SD score	BMI (kg/m^2)	Adrenal androgens at PP diagnosis[a]		
				Δ^4-A (ng/dL)	DHEAS(μg/dL)	Post-ACTH 17-OHP (ng/dL)
B1						
PP (n = 22)	7.0 ± 0.2	1.0 ± 0.2	17.8 ± 0.5	129.8 ± 9.4	122.7 ± 10.5	258.3 ± 29.8
C (n = 18)	7.9 ± 0.3	−0.3 ± 0.2	16.5 ± 0.3			
B2						
PP (n = 18)	10.0 ± 0.2	1.2 ± 0.3	21.0 ± 0.6	141.1 ± 10.6	105.2 ± 8.3	271.2 ± 27.1
C (n = 10)	11.0 ± 0.3	0.1 ± 0.2	18.7 ± 0.6			
B3						
PP (n = 14)	11.1 ± 0.2	1.0 ± 0.1	20.8 ± 0.4	159.8 ± 10.9	111.0 ± 9.8	251.3 ± 30.6
C (n = 24)	12.4 ± 0.2	−0.3 ± 0.3	19.4 ± 0.5			
B5						
PP (n = 48)	14.5 ± 0.3	0.2 ± 0.2	22.1 ± 0.3	141.3 ± 11.9	126.0 ± 9.1	236.1 ± 21.2
C (n = 31)	14.7 ± 0.2	−0.4 ± 0.2	20.7 ± 0.4			

Values are the mean ± SEM. B1–B5, Tanner breast stages I–V; PP, precocious pubarche; C, controls; CA, chronological age; BMI, body mass index; Δ^4-A, androstenedione; DHEAS, dehydroepiandrosterone sulfate.

[a] Normal values for control prepubertal girls (mean ± SEM; n = 240): Δ^4-A, 68.7 ± 2.8 ng/dL; DHEAS, 36.0 ± 13 μg/dL; post-ACTH 17-OHP, 198.2 ± 11.5 ng/dL.

TABLE 2. Hirsutism scores, SHBG levels, and androgen levels in postmenarcheal precocious pubarche girls with ovarian hyperandrogenism (FOH) and without ovarian hyperandrogenism (non-FOH)

	Ferriman-Gallwey score	SHBG (μg/dL)[a]	T (ng/dL)[a]	Δ^4-A (ng/dL)[a]	DHEAS (μg/dL)[a]	Postleuprolide acetate 17-OHP (ng/dL)[a]
FOH (n = 23)	14.2 ± 0.9	1.1 ± 0.1	54.5 ± 4.3	322.6 ± 38.3	212.1 ± 20.4	226.7 ± 7.9
Non-FOH (n = 25)	8.1 ± 0.5	0.9 ± 0.1	42.5 ± 3.5	212.3 ± 13.7	167.8 ± 16.3	90.3 ± 3.8

SHBG, Sex hormone-binding globulin; T, testosterone; Δ^4-A, androstenedione; DHEAS, dehydroepiandrosterone; 17-OHP, 17-hydroxyprogesterone.

[a] Normal values for control postmenarcheal girls (mean ± SEM; n = 47): SHBG, 1.0 ± 0.1 μg/dL; T, 30.6 ± 1.0; Δ^4-A, 140.4 ± 3.6; DHEAS, 132.1 ± 2.7; postleuprolide acetate 17-OHP, 90.5 ± 2.5.

test was performed in all subjects, starting at 0800 h. Blood was sampled 0, 30, 60, and 120 min after oral glucose administration for glucose and immunoreactive insulin measurements, as previously described (2, 3, 19). All samples were immediately centrifuged, and serum was separated and frozen at −20 C until assayed.

All subjects had normal glucose tolerance according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus criteria (20).

The areas under the curve for glucose (mean serum glucose) and insulin [mean serum insulin (MSI)] were calculated according to the trapezoidal rule. A MSI value above 54 mU/L in prepubertal patients and above 84 mU/L in pubertal patients was considered abnormal (21).

Birth weight and gestational age data for both patients and controls were obtained from hospital records and transformed into SD scores according to 1997 Flemish references (correction factor of 0.9714 for all birth weights) (8).

Hormone assays

Serum glucose was measured by the glucose oxidase method. Immunoreactive insulin was assayed by IMX (Abbott Diagnostics, Santa Clara, CA). The mean intra- and interassay coefficients of variation were 4.7% and 7.2%, respectively. Serum steroid concentrations (T, 17-OHP, DHEAS, and Δ^4-A) were determined using commercially available RIA kits (2), and serum SHBG was measured by RIA using monoclonal anti-SHBG antibodies, as previously described (19).

Statistical analysis

Anthropometric data and hormonal results are expressed as the mean ± SEM unless otherwise stated. Variables among independent groups were compared by one-way ANOVA corrected by Scheffe's test for multiple comparisons. Analysis of covariance was performed to assess the contribution of BMI to the differences in the hormonal parameters tested between patients and controls. $P < 0.05$ was considered significant. Correlations were examined by linear regression analysis.

Results

Birth weight SD scores of control girls (0.38 ± 0.08) were higher ($P < 0.0001$) than those of PP girls (−0.81 ± 0.13; Fig. 1), whereas gestational ages were similar (39 ± 0.1 *vs.* 39 ± 0.2 weeks). Among postmenarcheal PP girls, birth weight SD scores of girls without FOH (−0.25 ± 0.19) were higher ($P < 0.0001$) than those of girls with FOH (−1.51 ± 0.28).

MSI levels were significantly higher in PP girls than in controls at all pubertal stages tested, as expected [B1, 45.9 ± 5.7 *vs.* 26.4 ± 2.3 ($P < 0.0001$); B2, 79.7 ± 10.0 *vs.* 46.6 ± 4.4 ($P < 0.001$); B3, 50.7 ± 5.1 *vs.* 42.5 ± 2.5 ($P = 0.01$); B5, 79.6 ± 7.3 *vs.* 41.7 ± 2.1 ($P < 0.0001$), respectively]. These differences persisted after adjusting for BMI. MSI values for control girls were similar to those previously reported (21).

MSI levels in girls with birth weight below 1 SD (93 ± 9 mU/L; n = 33) were higher ($P < 0.0001$) than those in girls with birth weight between −1 and +1SD (52 ± 2 mU/L; n = 94), whereas mean serum glucose concentrations were comparable (6.6 ± 0.2 *vs.* 6.2 ± 0.2 mmol/L, respectively).

In pubertal girls (n = 145), MSI levels correlated negatively with birth weight SD scores ($r = -0.48$; $P < 0.05$), independently of PP.

When the PP and FOH results in postmenarcheal girls were integrated with the MSI results, it became apparent that there was a sequence in the associations between reduced prenatal growth and the studied components of the postnatal endocrine system; amplification of adrenarche was followed by FOH, and, finally, by insulin hyperresponsiveness, suggestive of insulin resistance (Fig. 2).

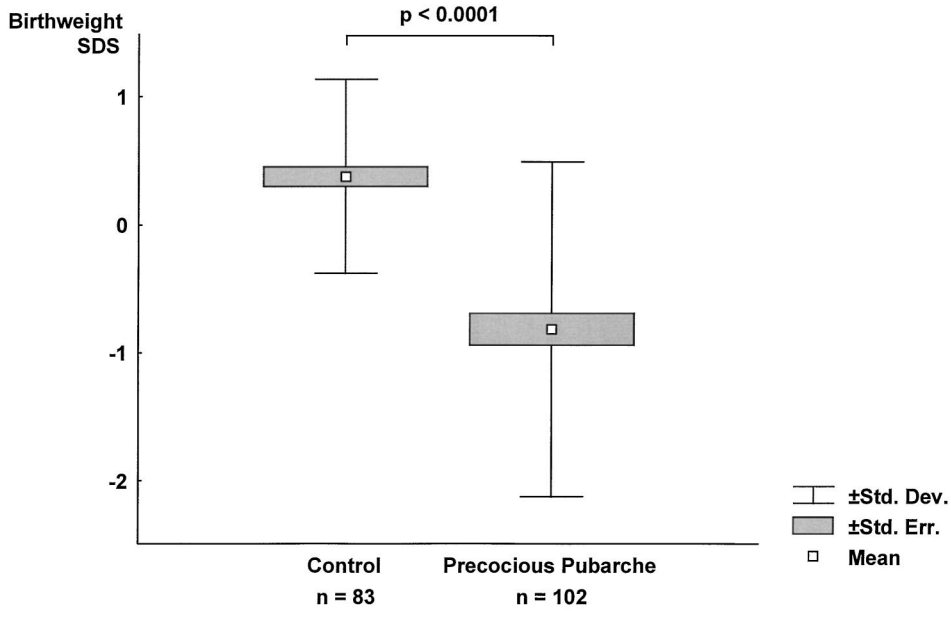

FIG. 1. Birth weight SD scores of control girls and patients with precocious pubarche.

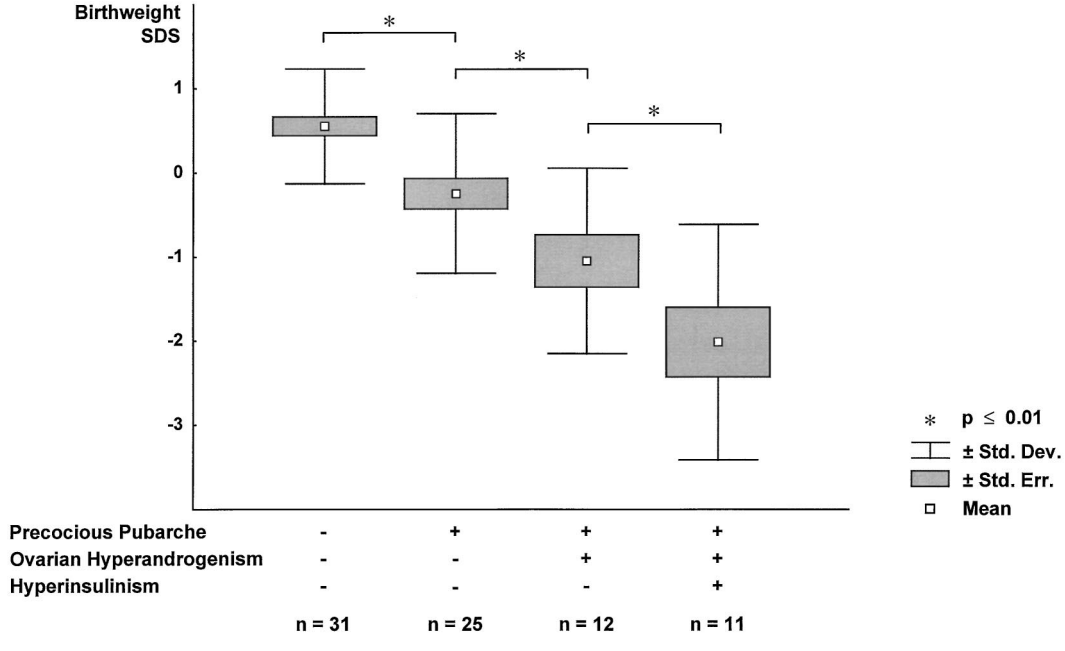

FIG. 2. Birth weight scores of postmenarcheal control girls (−, −, and −) and postmenarcheal girls with a history of precocious pubarche without ovarian hyperandrogenism and without hyperinsulinemia (+, −, and −), with ovarian hyperandrogenism and without hyperinsulinemia (+, +, and −), and with both ovarian hyperandrogenism and hyperinsulinemia (+, +, and +).

Discussion

Our results indicate that girls with a history of PP during childhood have low birth weight SD scores and that this is particularly so in those girls who subsequently develop idiopathic FOH. Moreover, insulin responses to a glucose load are higher in pubertal girls with lower birth weights. Together, these findings suggest that PP, FOH, and definite insulin hyperresponsiveness may represent, in that order, a sequence of endocrine modulations that is associated with increasing severity of prenatal growth restrictions.

Although the frequent concurrence of PP (with pronounced adrenarche), hyperinsulinism, and ovarian hyperandrogenism has been well documented in adolescent girls (1–3, 22), the mechanisms interlinking this triad remain enigmatic (23, 24). The present results point to separate relations between reduced fetal growth and PP, hyperinsulinism, and ovarian hyperandrogenism, indicating that this triad may at least in part result from a common early origin rather than from a direct interrelationship initiated in late childhood or adolescence.

Reduced fetal growth has first been related to noninsulin-dependent diabetes mellitus in older adults (25). Subse-

quently, reduced fetal growth was found to be associated with insulin resistance in short prepubertal children (7). The present insulinemia results after standardized glucose tolerance testing provide evidence to extend the latter relationship not only into adolescence, but also into the quantitatively more important group of those children who display postnatal catch-up growth after prenatal growth restriction. In addition, the magnitude of the difference in insulin responses between the low and normal birth weight groups (a factor of nearly 2) was similar in short prepubertal children (7) and in the present cohort.

Low birth weight has long been known to be associated with hypoplasia of the fetal adrenal zone and with lower fetal serum concentrations of DHEAS (26, 27). Judged by serum DHEAS levels, adrenarche has recently been found to be more pronounced in children born small for gestational age, specifically in those who displayed postnatal catch-up growth (6). The present results point to the clinical relevance of the former by extending the relation between reduced fetal growth and exaggerated adrenarche to the clinical entity of PP.

Reduced fetal growth has previously been associated with human gonadal dysfunction, specifically with subfertility in males (8), which is thought to be to some extent attributable to a quantitative loss of Sertoli cells in early life (28). The association between reduced fetal growth and gonadal dysfunction is hereby extended to include ovarian hyperandrogenism in postmenarcheal girls. The average degree of prenatal growth reduction observed in the present series of girls with the sequence of PP and ovarian hyperandrogenism was strikingly more pronounced than that in girls with PP without ovarian hyperandrogenism. These findings can be interpreted as indicating that pubertal ovarian steroidogenesis is either less sensitive to prenatal modulation (*i.e.* requires more growth restriction) than adrenal androgen production, or that ovarian hyperandrogenism was hitherto not as readily recognized by clinical and/or endocrine screening procedures.

The separate relationships between low birth weight and PP, hyperinsulinemia, and ovarian androgen excess could be due to different and independent mechanisms, or there may be a common mechanism. For example, hormonally regulated serine phosphorylation of adrenal cytochrome P450c17α by a cAMP-dependent kinase accounts for a large increase in 17,20-lyase activity and has been proposed as the mechanism for normal adrenarche (29, 30). Insulin-like growth factor I (IGF-I) has been suggested as the physiological trigger for this process, as its serum levels rise and fall in a pattern that is contemporaneous with DHEAS secretion (29). The insulin receptor also may be phosphorylated on serine residues of the β-chain. (31, 32). This serine phosphorylation can diminish or block the insulin-induced tyrosine autophosphorylation needed for insulin signal transduction (33). Approximately half of women with PCOS have insulin receptors with higher levels of β-chain serine phosphorylation, strongly suggesting that this mechanism accounts for the insulin resistance of a substantial portion of the PCOS population (34, 35). Therefore, an abnormality in serine phosphorylation, possibly associated with a single kinase, may be responsible for excessive serine phosphorylation of the insulin receptor and P450c17α, leading to insulin resistance and hyperandrogenism (30, 35, 36).

Finally, in view of the importance of insulin as a fetal growth factor (37), it is conceivable that abnormal serine phosphorylation of the insulin receptor may be also primarily involved in reduced fetal growth. Thus, a defect in serine kinase activity would be the first hypothetical mechanism that could explain the sequence of reduced fetal growth, hyperinsulinism, pronounced adrenarche with PP, and subsequent ovarian hyperandrogenism.

Other mechanisms by which reduced fetal growth may be related to hyperinsulinemia and subsequently adrenal and ovarian hyperandrogenism are presently unclear. It has been postulated that fetal adaptation to an adverse intrauterine environment involves altered programming of endocrine pathways, leading to permanent metabolic changes (38). Colle *et al.* reported a positive correlation between catch-up growth of infants with reduced fetal growth and insulin responses to iv glucose tolerance testing as early as 6 months of age (39). Whether this increased insulin secretion, if sustained, may further augment linear growth, a clinical feature characteristic of PP with pronounced adrenarche (40), and subsequently enhance adrenal steroidogenesis (41) is currently unknown. Along the same line, receptors for important fetal growth factors, such as insulin, IGF-I, and IGF-II, are known to be present in human fetal ovaries (42). Hyperinsulinemia increases ovarian androgen production, presumably acting through the ovarian insulin or IGF-I receptors (43–45). It remains to be established whether a disturbance of intraovarian peptide signaling during fetal life may have a long term impact on ovarian function.

Regardless of the precise mechanisms involved, it is clear that further research into the pathogenesis of the aforementioned triad should envisage the possibility of an early origin and, accordingly, no longer be restricted to the adolescent or adult phase of life.

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