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Prematurity May Be a Risk Factor for Thyroid Dysfunction in Childhood

Giorgio Radetti, Antonio Fanolla, Lucia Pappalardo, and Elena Gottardi

Departments of Paediatrics (G.R., L.P., E.G.) and Biostatistics (A.F.), Regional Hospital of Bolzano, 39100 Bolzano, Italy

Context: Children born prematurely and/or small for gestational age (SGA) frequently show disturbances in thyroid function.

Objective: The objective of the study was to determine the role played either by size or gestational age on subsequent thyroid function.

Design and Setting: This cross-sectional study was conducted at a tertiary referral hospital.

Patients: A total of 117 children, 88 of whom were SGA (mean age 7.8 ± 2.5 yr) and 29 appropriate for gestational age (AGA) (mean age 8.1 ± 1.9 yr), were selected for the study.

Main Outcome Measures: We evaluated TSH, free T_4, free T_3, urinary iodine, and antithyroid antibodies, and all patients underwent a thyroid ultrasound. Insulin sensitivity was assessed with the quantitative insulin sensitivity check index.

Results: TSH and free T_3 were not significantly different in the two groups, whereas free T_4 was higher in the AGA group ($P < 0.005$). Interestingly, four AGA (13.8%) and 17 SGA (19.3%) patients had TSH levels above the upper limit of normality. Thyroid volume was normal and thyroid autoimmunity was excluded. Urinary iodine was also similar in the two groups (115 ± 66 *vs.* 143 ± 87); however, in both groups there were some children [15 AGA (51%) and 13 SGA (14.7%) ($P < 0.001$)] with a mild to moderate iodine deficiency. By multiple regression analysis, gestational age was found to be the only determinant of TSH serum levels. Insulin sensitivity was the same in both groups of children and similar to controls.

Conclusions: Some children born prematurely, independently from their birth size, frequently have disturbances of the hypothalamus-pituitary-thyroid axis later in life. **(*J Clin Endocrinol Metab* 92: 155–159, 2007)**

INTRAUTERINE GROWTH retardation has been unequivocally associated with the development of adult diseases such as higher systolic blood pressure (1, 2), increased cardiovascular mortality (3), elevated plasma cortisol (4), glucose intolerance, hyperinsulinism, and type 2 diabetes (5, 6) and also with premature pubarche and ovarian hyperandrogenism (7). Moreover, we recently reported that thyroid function is frequently altered in children born small for gestational age (SGA) (8). The aim of the present study was to confirm this finding in a larger number of children and in particular to verify the role played by prematurity *per se* on thyroid function later on in life.

Subjects and Methods

We selected for the study 117 children (63 females, 54 males) who at the time of the investigation were 7.9 ± 2.4 yr old, and we subdivided them according to their neonatal status. Twenty-nine (15 females) were born appropriate for gestational age for length and weight (AGA) and 88 (48 females) SGA; SGA was defined as weight and length at birth below the 10th centile, according to Lubchenko *et al.* (9). All these children were born at our hospital between 1995 and 2004 and were all admitted to the neonatal intensive care unit because of prematurity and/or growth restriction. They have all been regularly followed up in our clinics. They represent the first 117 consecutive patients whose parents gave their consent to participate to the study. The AGA children were all premature, with a gestational age of 32 ± 1 (27–34) wk, weight 1744 ± 320 (1200–2450) g, and length 42 ± 1.8 (38–45) cm; the SGA group of children had a gestational age of 35 ± 3 (28–41) wk, weight 1686 ± 481 (570–2420) g, and length 42 ± 4 (30–48) cm. Fifty-six children in the SGA group were born prematurely. The length of the newborns was assessed by a neonatal infantometer. The auxological features of both groups of children at the time of the investigation are reported in Table 1. Children with central nervous system disorders as well as ex-premature subjects affected with bronchopulmonary dysplasia were excluded from the study. During pregnancy all mothers followed a well-balanced and healthy diet, and only seven of them smoked two to three cigarettes a day. Data regarding smoking were available from only 98 mothers. The great majority of the mothers were employed as teachers or office workers.

An informed consent for the study was obtained from the parents of all children, and the study protocol was approved by the Ethical Committee of our hospital.

Study protocol

The children were admitted to the hospital between 0800 and 0900 h after an overnight fast for evaluation of thyroid function [free T_4 (fT4), free T_3 (fT3), antithyroid antibodies], TSH serum levels, urinary iodine, and auxological parameters; moreover, they all underwent a thyroid ultrasound on the same day.

Weight and length at birth were converted, for statistical purposes, to SD scores (SDS), according to Usher and McLean (10), whereas the actual height was expressed as SDS, according to Tanner *et al.* (11). Nutritional status at birth was assessed with the ponderal index (grams per cubic centimeter × 100) (12), whereas at the time of the study, it was expressed as body mass index (BMI) (kilograms per square meter) SDS (13).

Insulin sensitivity was evaluated with the quantitative insulin sensitivity check index (QUICKI) $(1/[\log(I_0) + \log(G_0)])$, where I_0 is the fasting insulin and G_0 the fasting glucose (14).

The atherogenic index (total/high-density lipoprotein-cholesterol), which is considered an index of severe cardiovascular risk (15), was also calculated.

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Abbreviations: AGA, Appropriate for gestational age for length and weight; BMI, body mass index; CV, coefficient of variation; fT3, free T_3; fT4, free T_4; QUICKI, quantitative insulin sensitivity check index; SDS, SD score; SGA, small for gestational age.

TABLE 1. Auxological features and thyroid function in SGA and AGA children at the time of investigation

	Age (yr)	Height SDS	BMI SDS	TSH (mU/liter)	fT4 (pmol/liter)	fT3 (pmol/liter)	TG-Ab	TPO-Ab
SGA (all)	7.8 ± 2.5	0.3 ± 1.1[a]	0.0 ± 1.7[b]	3.2 ± 1.7	14.8 ± 2.3[c]	6.6 ± 1.5	–	–
SGA younger than 37 wk	7.4 ± 2.2	0.2 ± 0.9	−0.1 ± 1.6	3.7 ± 2.0	15.3 ± 2.2	6.5 ± 0.6	–	–
SGA older than 37 wk	9.1 ± 2.8	0.4 ± 1.2	0.1 ± 2.1	2.6 ± 0.9	14.0 ± 3.3	6.4 ± 0.7	–	–
AGA	8.1 ± 1.9	0.8 ± 0.9	1.1 ± 1.9	3.1 ± 1.2	16.2 ± 2.3	6.4 ± 0.6	–	–

TG-Ab, Thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody.
[a] $P < 0.05$ for the difference between the SGA (all) and AGA groups.
[b] $P < 0.01$ for the difference between the SGA (all) and AGA groups.
[c] $P < 0.005$ for the difference between the SGA (all) and AGA groups.

Thyroid ultrasound was performed by the same observer (L.P.) with a 7.5-MHz transducer. The findings were compared with the normal ones for the same population (16)

Assays

TSH was measured by RIA (DiaSorin, Dietzenbach, Germany); the intra- and interassay coefficients of variation (CVs) were 2.5 and 5.7%, and the sensitivity limit was 0.02 mIU/ml. fT3 was measured by RIA (DiaSorin); the intra- and interassay CVs were 4.6 and 6.5%, and the sensitivity limit was 0.35 pg/ml. fT4 was measured by RIA (DiaSorin); the intra- and interassay CVs were 2.4 and 6.8%, and the sensitivity limit was 1 pg/ml. Thyroglobulin antibodies were measured by immunoradiometric assay (DiaSorin) with an intra- and interassay CV of 4.1 and 5.2% and a sensitivity limit of 2 U/ml; thyroid peroxidase antibodies were measured by RIA (Biocode, Liege, Belgium) with an intra- and interassay CV of 4.8 and 6.2% and a sensitivity limit of 1 U/ml. Iodine urinary excretion was measured on a morning urine spot by mass spectrography, according to the ICP method (PerkinElmer, Norwalk, CT). Serum glucose level was measured with automatic analyzers, using an hexokinase catalyzed-glucose oxidase method. Serum insulin was measured with an immunoradiometric assay (Immulite 2000 insulin; Diagnostic Products Corp., Los Angeles, CA), which has an intra- and interassay CV of 8.3 and 8.6%, respectively, and a sensitivity limit of 2 μIU/ml. Serum IGF-I was assessed with an immunoradiometric assay (Immulite 2000 insulin; Diagnostic Products Corp.) with an intra- and interassay CV of 3.0 and 6.2%, respectively, and a sensitivity limit of 2.6 nmol/liter. Total and high-density-lipoprotein cholesterol and triglycerides were measured enzymatically by an automatic photometric method (Olympus Diagnostica Gmbh, Lismeehan, O'Callaghan's Mills, Co. Clare, Ireland).

Statistical analysis

Data are expressed as mean ± SD. Differences between means were assessed by using an unpaired Student's *t* test, whereas the difference in frequency between groups was verified with the Fisher's exact test. The correlation between variables was sought by calculating the Pearson coefficient after ascertaining that the values were normally distributed. Forward stepwise regression analysis was used in the selection of predictors of TSH. All the analyses were performed with the SPSS statistical program (version 12.01; SPSS, Inc., Chicago, IL) in all calculations. $P < 0.05$ was considered statistically significant.

Results

Auxology

At birth, length SDS in the SGA group was −2.4 ± 1.5, weight SDS −2.3 ± 0.9, and ponderal index 2.2 ± 0.2, whereas in the AGA group, length SDS was −0.4 ± 0.9, weight SDS −0.1 ± 0.9, and ponderal index 2.3 ± 0.3. At the time of the study (Table 1), height SDS was significantly greater in the AGA group ($P < 0.05$); however, in both groups height was normal for age. In particular, no one had a height SDS of less than −2 SDS, showing that all children had a full catch-up growth. The height gain, calculated as the difference between the actual height SDS and the length SDS observed at birth, was significantly greater in the SGA group, compared with the AGA group (2.37 ± 1.71 *vs.* 1.24 ± 1.12; $P < 0.001$). BMI SDS was normal in all children but higher, however, in the AGA group ($P < 0.01$). The clinical and laboratory data of the SGA group, subdivided according to the gestational age, are reported in Table 1.

Thyroid function

TSH and fT3 were not significantly different in the two groups (Table 1), but fT4 was higher in the AGA group ($P < 0.005$). Interestingly, four AGA (13.8%) and 17 SGA (19.3%) children had TSH levels above the upper limit of normality (4.2 mU/liter), with values ranging from 4.3 to 10.76 mU/liter; Fig. 1). The frequency of altered TSH levels was similar in the two groups but much higher, however ($P < 0.05$), than the frequency of 5.2% found in a survey of 916 schoolchildren conducted in our region (16), where the main cause for the elevated TSH was Hashimoto's thyroiditis diagnosed, however, in the older subgroup of the cohort examined.

In our study thyroid autoimmunity in those with elevated TSH levels was excluded by the absence of thyroid antibodies and a normal echographic pattern. Thyroid volume was similar in the two groups (AGA 2.6 ± 0.8 *vs.* SGA 3.2 ± 2.0 ml; not significant) and always in the normal range (16). Urinary iodine was also similar in the two groups (115 ± 66 *vs.* 143 ± 87 μg/liter); in both groups, however, there were some children, 15 AGA (51%) and 13 SGA (14.7%) ($P < 0.001$ for the difference), who had a mild (50–100 μg/liter) to moderate (25–50 μg/liter) iodine deficiency. The range of urinary iodine was 46–500 μg/liter in the SGA group and 22–284 μg/liter in the AGA group.

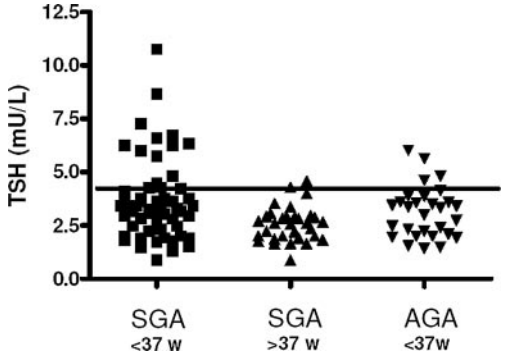

FIG. 1. TSH serum levels in the SGA and AGA groups.

IGF-I was 20.7 ± 11.6 nmol/liter in the SGA group and 21.6 ± 9.0 nmol/liter in the AGA group (not significant).

Insulin sensitivity (QUICKI), was the same in both groups of children: AGA (0.38 ± 0.04) and SGA (0.38 ± 0.05) and within our normal values (<0.380 ± 0.04) (17).

Lipids

No differences were found between AGA and SGA children in relation to triglyceride values (0.82 ± 0.37 *vs.* 0.81 ± 0.46 mmol/liter), total cholesterol (4.37 ± 0.69 *vs.* 4.55 ± 0.82 mmol/liter), high-density lipoprotein-cholesterol (1.60 ± 0.31 *vs.* 1.56 ± 0.31 mmol/liter), and the atherogenic index (2.8 ± 0.7 *vs.* 3.0 ± 0.7). All these values were in the normal range for our laboratory.

Correlations

The actual height was correlated with IGF-I ($r = 0.47$; $P < 0.000$), insulin ($r = 0.27$; $P < 0.01$), thyroid volume ($r = 0.49$; $P < 0.00$), and BMI ($r = 0.36$;$P < 0.00$). Height gain was correlated with birth length SDS ($r = -0.79$; $P < 0.000$), birth weight SDS ($r = -0.52$; $P < 0.000$), and ponderal index ($r = 0.41$; $P < 0.000$). TSH was negatively correlated with gestational age ($r = -0.262$; $P = 0.004$) (Fig. 2) and ponderal index ($r = -0.207$; $P < 0.05$) but with neither length-SDS at birth nor fT4. Forward stepwise regression analysis with TSH as the dependent variable and gestational age, birth length SDS, birth weight SDS, ponderal index, fT4, insulin, QUICKI, and urinary iodine showed that gestational age was the only parameter able to influence TSH serum levels (adjusted $r^2 = 0.13$; $P = 0.003$), $y = 8.76 - 0.167$*EG. This is also confirmed by the fact that if we subdivide the whole group (AGA+SGA) according to whether they have a TSH less than 4.2 mU/liter (93 patients) or greater than 4.2 mU/liter (24 patients), the only parameter significantly different between the two groups is gestational age (35 ± 3 *vs.* 33 ± 2 wk; $P < 0.05$).

QUICKI was significantly correlated with height SDS ($r = -0.42$; $P < 0.005$), BMI SDS ($r = -0.5$; $P < 0.001$), and triglycerides ($r = -0.3$; $P < 0.01$). The atherogenic index was correlated only with triglyceride values ($r = 0.7$; $P < 0.001$).

Smoking during pregnancy was associated with a higher frequency of raised TSH in the offspring ($P < 0.05$).

Discussion

The present study, conducted in a large group of patients born either preterm or at term, clearly shows that children born prematurely, independently from their birth weight or length, frequently present with disturbances of the hypothalamus-pituitary-thyroid axis later in life. In a previous study, in which we examined a group of children of the same age, we found an increased prevalence of thyroid dysfunction in those born SGA (8) and identified in the shorter length at birth the cause for the thyroid alteration. In that study, however, most of the patients were born prematurely, and there was indeed a trend toward a negative correlation between TSH levels and gestational age, which, however, did not reach statistical significance, probably because of the low number of patients examined. In this study, with a larger number of subjects investigated, we can clearly show that gestational age is the only factor influencing TSH levels. The demonstration that gestational age and not weight or length at birth is the main determinant of TSH level in childhood is in agreement with the data of Cianfarani *et al.* (18), who showed that SGA children born at term, although having higher TSH values, compared with controls, all had TSH levels within normal range. This further confirms the fact that gestational age and not intrauterine growth restriction is the main cause for the TSH alterations, as clearly shown in Fig. 1, in which the group of SGA children, subdivided according to the gestational age, is compared with the AGA group, including only children born prematurely.

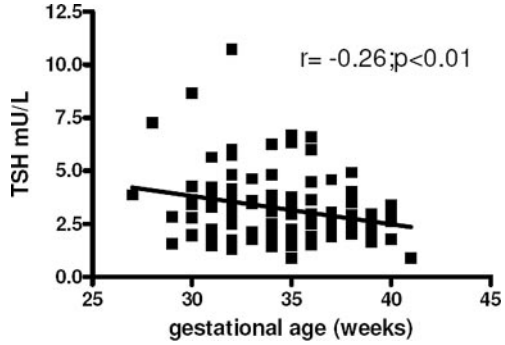

FIG. 2. Relationship between TSH levels and gestational age.

What causes the alteration in the hypothalamus-pituitary-thyroid axis is still unknown. Thyroid autoimmunity was excluded by the absence of thyroid autoantibodies together with a normal echographic pattern. Factors interfering with gland growth and differentiation can almost certainly be excluded because thyroid morphology and volume were also normal on ultrasound examination.

We found that mothers who smoked during pregnancy more frequently had children with raised TSH, compared with those who did not (0.57 *vs.* 0.15%; $P < 0.05$); however, only seven mothers (7.1%) smoked, and therefore, it is quite difficult to draw any conclusions from such a small number. Smoking has often been reported to cause Grave's disease, Grave's ophthalmopathy, toxic and nontoxic nodular goiter, but not hypothyroidism (19)

Other possible explanations for the raised TSH might not be the result of thyroid impairment but rather an altered feedback at hypothalamic-pituitary level. Recently a significant reduction of the expression of thyroid receptors isoforms in the cerebral cortex and cerebellum of fetuses with intrauterine growth restriction has been described (20). If a reduced mRNA expression of thyroid receptors were present also in the hypothalamic-pituitary area, then this would explain the reset of TSH sensitivity at central level. Moreover, we wonder whether the lack of correlation between TSH and fT4 could be due to an altered sensitivity at hypothalamic-pituitary level. Children involved in the study were not severely obese, a condition that may be associated with an abnormal thyroid function in children and adults (21–23). Furthermore, a mild to moderate degree of iodine deficiency was detected in the ex-premature children, particularly in the AGA group, which was not correlated with TSH levels and unlikely to be responsible for the raised TSH. Premature babies are known to be at risk for iodine deficiency in the neonatal period (24), but there are no data showing that the iodine deficiency would persist in the following years. More-

over, a better assessment of the iodine status should be based on a 2- to 3-d urine collection, in view of the large day-to-day variations in urinary iodine output. If our data are going to be confirmed by further studies, then screening the ex-premature infants for iodine deficiency should be considered. There is a possibility, in fact, that a concomitant iodine deficiency could negatively influence their neuromotor and cognitive abilities (25, 26) and potentially worsening, in some instances, their already poor educational achievement (27, 28). Altogether the finding of altered TSH values in ex-premature children closely resembles the occurrence of a reduced insulin sensitivity, which was at first considered a typical feature of ex-SGA children and ultimately found to be a consequence of prematurity *per se* more than the outcome of intrauterine growth restriction (29).

Regarding insulin resistance, we can confirm our previous results (8) because we did not find in the children involved in this study any signs of a reduced insulin sensitivity. This finding is at variance with some studies (30, 31) but in accordance with another one (18), suggesting that an impaired insulin sensitivity, a hallmark of the metabolic syndrome, might not be an obligatory feature of children born SGA. There is a possibility, however, of a further derangement of insulin sensitivity over time, as already reported in adults (5).

Both ex-AGA and -SGA children experienced a full catch-up growth and had a normal stature for their age at the time of the study, and in particular none of them had a stature below −1.9 height SDS. As expected, height gain was more pronounced in the SGA group, compared with the AGA group ($P < 0.01$). IGF-I, BMI, and insulin were found to be positively correlated with the actual height. Insulin, in particular, is strictly related with BMI and is known to positively affect growth velocity by modulating several components of the IGF-IGF binding protein system (32, 33) by allowing a higher bioavailability of IGF-I to the target tissue. A pronounced postnatal catch-up growth has been linked to insulin resistance in adulthood (34). In our patients, however, no signs of insulin resistance were found, not even in those with the greatest postnatal catch-up growth. Ex-SGA children with appropriate catch-up growth do not therefore seem to be necessarily destined to have a permanent derangement in glycemic homeostasis, as previously reported (18).

Despite the reported alterations in thyroid function, none of the children ever had any related signs or symptoms. A longitudinal follow-up survey is, however, mandatory to clarify whether the reported thyroid dysfunction might eventually lead to a state of overt hypothyroidism.

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Address all correspondence and requests for reprints to: Dr. Giorgio Radetti, Department of Paediatrics, Regional Hospital, via L. Boehler 5, 39100 Bolzano, Italy. E-mail: giorgio.radetti@asbz.it.

The authors have nothing to disclose.

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