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ORIGINAL ARTICLE

# Altered thyroid function in small for gestational age newborns: study based on screening test for congenital hypothyroidism

Franco Bagnoli[1], Laura Farmeschi[1], Luana Peruzzi[1], Antonietta Musarò[1], Patrizia Paffetti[1], Silvia Badii[1], Martina Casucci[1], Letizia Pasqui[2], Francesca Iacoponi[3]

***Abstract:***

**Background and Aims:** Unequivocal data is not yet available on alterations in plasma concentrations of thyroid hormones that may characterize small-for-gestational-age (SGA) newborns. We used data from screening for congenital hypothyroidism in a large population to evaluate the relationship between growth restriction and thyroid function in the first week of life.

**Materials and Methods:** Subjects: 14,092 newborns (13,333 appropriate-for-gestational-age (AGA) and 759 SGA) screened for congenital hypothyroidism on the third day of life. The screening test measured plasma concentrations of TSH and T4 by fluoroimmunoenzyme assay.

**Results:** Comparison of SGA and AGA newborns revealed lower serum concentrations of T4 in preterm and term SGA infants (P=0.0001), whereas concentrations of TSH were significantly higher only in term SGA infants (P=0.0001). T4 concentrations were positively correlated with gestational age in SGA and AGA groups, whereas TSH concentrations were only correlated with gestational age in the AGA group. 1.84% of SGA babies were recalled for TSH and T4 anomalies against only 0.93% of AGA newborns (p=0.01).

**Conclusion:** SGA babies had a higher incidence of transient hypothyroidism and required accurate follow-up and close monitoring of thyroid function.

***Keywords:*** newborn, SGA, screening, TSH, T4
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## Introduction

Babies with a birth weight and/or length below the 10th percentile of a population of the same gestational age are defined small-for-gestational-age (SGA) [1, 2]. There may be many causes of intrauterine growth retardation and birth of SGA babies. Various pathophysiological mechanisms and endocrine-metabolic alterations characterize this condition [1, 3-5]. These alterations may affect neonatal adaptation and future health in infancy and adulthood: indeed, higher incidences of pathologies such as cardiovascular events, metabolic syndrome, hypertension and obesity have been demonstrated [6-12]. Few studies have compared thyroid function in SGA and appropriate-for-gestational-age (AGA) newborns. Conflicting results have been published for neonatal plasma concentrations of T4 and TSH, though the papers are difficult to compare because

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the assays were conducted at different times (in cord blood at birth, in the first days, in the first weeks) and by different methods [13-18]. Thyroid hormones are fundamental for growth and neurocognitive development. A relationship between hormone alterations, growth retardation and related conditions has yet to be established, in particular whether alterations in thyroid function may be a cause or consequence of growth retardation.

To our knowledge, there has been no study using screening tests for congenital hypothyroidism to determine the existence of altered thyroid function in SGA newborns in the first week of life. To assess any alterations in plasma concentrations of T4 and TSH in SGA newborns, we analyzed a large population of babies born in 2004 and 2005 in the area served by Siena University Hospital. We used the results of the screening test for congenital hypothyroidism conducted routinely on the third day of life. Although we realized the limits of a study based on a screening test, we reasoned that assessment on the third day could exclude alterations of these hormones due to the birth event, type of delivery and any fetal hypoxia. We also considered this to be the only valid approach for examining a very large population from a given area based on a blood sample drawn on the third day.

**Material and Methods**

We analyzed the screening tests for congenital hypothyroidism of 14,092 newborns from the Siena area, with gestational ages in the range 23-42 weeks (mean gestational age 39.2 weeks) and birthweights in the range 440-5400 g (mean weight 3268.7 g), from 1st January 2004 to 31st December 2005.
The population was divided into two groups:

AGA babies: 13,333 newborns with a mean gestational age of 39.2 weeks and mean birthweight of 3286 g. The group included 11,843 term and 1490 premature babies (11.17%). Newborn infants born before completing 37 weeks of gestation were considered premature.

SGA babies: 759 newborns with a mean gestational age of 39.6 weeks and mean birthweight of 2577.7 g. The group included 705 term and 54 premature babies (7.11%). 370 SGA babies were under the third percentile and 389 were between the 3rd and 10th percentile. The data of the population is summarized in Table 1.

**Table 1. The data of the population.**

| | TOTAL | AGA | SGA |
|---|---|---|---|
| **NUMBER** | 14092 | 13333 | 759 |
| **PRETERM** | 1544 | 1490 | 54 |
| **MEAN WEIGHT (g)** | 3268.7 ± 508.73 | 3286 ± 485.15 | 2577.7 ± 397.13 |
| **MEAN GESTATIONAL AGE (weeks)** | 39+2 ± 1.81 | 39+2 ± 1.81 | 39+6 ± 1.82 |

A comparison was also made by gender: 6891 newbors were females and 7201 were males.

The screening test was conducted on the third day of life by medial or lateral heel prick with a finger lance after disinfecting and drying the area of skin. Three drops of blood were collected on special filter paper and air-dried. The papers and patient details were sent to the laboratory of the Pediatrics Clinic for hormone screening. TSH was assayed by direct fluoroimmunoenzyme assay kit "DELFIA Neonatal hTSH" by Perkin-Elmer (Massachusetts USA). T4 was assayed by competitive fluoroimmunoenzyme assay kit "DELFIA Neonatal Thyroxine" by the same company.

**Statistical Analysis**

The data was expressed as median and interquartile range (IQR) or as frequencies and percentages (%). Normal distribution of the data was confirmed by the Kolmogorov-Smirnov test. Comparisons were calculated by the Mann-Whitney or chi-squared test. Correlations between hormone concentrations and gestational age were expressed with the Spearman coefficient. Values having $p<0.05$ were considered statistically significant. Graph Pad Prism software was used for all tests.

**Results**

Significantly higher plasma concentrations of TSH were found in the whole SGA population than in the

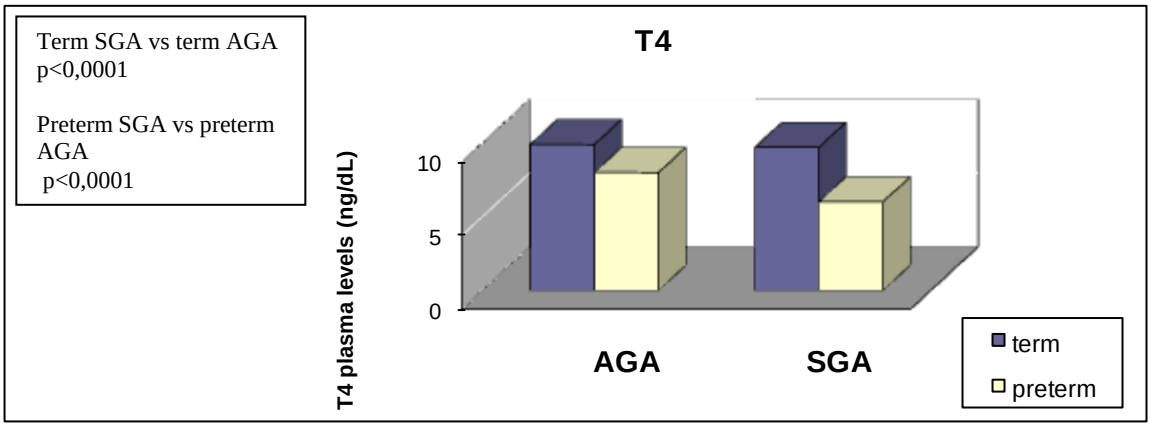



**Figure 1. Plasma concentrations of T4 in term and preterm AGA and SGA newborns**

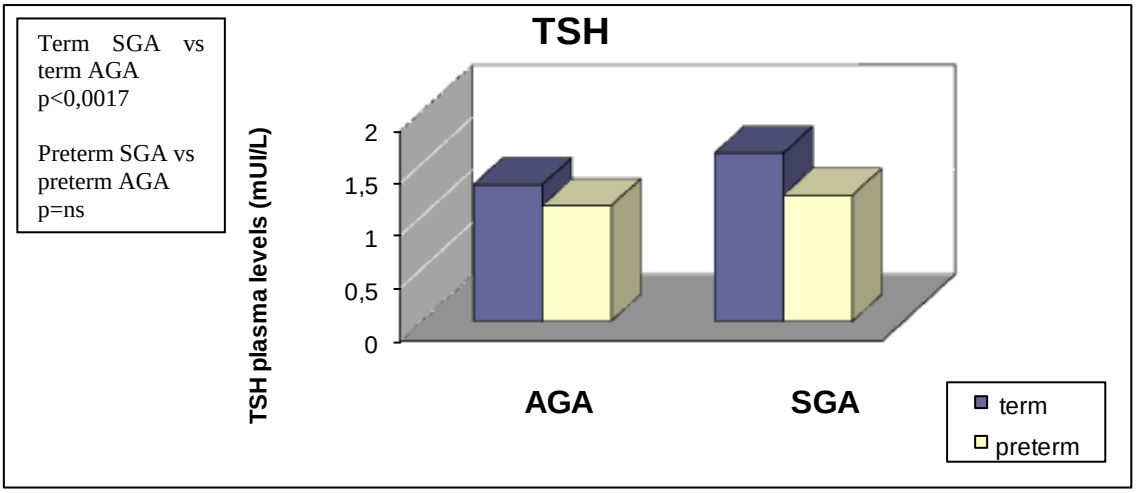



**Figure 2. Plasma concentrations of TSH in term and preterm AGA and SGA newborns**

AGA group (AGA: 1.3 (0.6-2.3) mIU/L; SGA: 1.6 (0.7-2.9) mIU/L; P<0.0001) together with significantly lower concentrations of T4 (AGA: 9.8 (8.3-11.4) ng/dL; SGA: 9.5 (8.1-11) ng/dL; P<0.0001). Term SGA babies had T4 concentrations significantly lower than term AGA babies (AGA: 9.9 (8.5-11.5) ng/dL; SGA: 9.7 (8.3-11.12) ng/dL; p<0.0001) and significantly higher TSH concentrations (AGA: 1.3 (0.6-2.4) mIU/L; 1.6 (0.8-3) mIU/L; p=0.0017) (Figs. 1 & 2). Preterm SGA newborns had significantly lower T4 concentrations than preterm AGA infants (AGA: 8.0 (6.2-9.6) ng/dL; SGA: 6.0 (4.7-7.8) ng/dL; P<0.0001); TSH did not show significant differences between the two groups, though it was lower in preterm SGA than in preterm AGA babies (AGA: 1.1 (0.4-2) mIU/L; SGA: 1.2 (0.6-1.7) mIU/L; p=0.69) (Figs. 1 & 2).

In the population of term newborns (AGA and SGA), T4 and TSH concentrations were significantly higher than in the population of preterm babies (AGA and SGA)(T4 term: 9.9 (8.5-11.5) ng/dL; T4 preterm:7.9(6-9.5) ng/dL; p< 0.0001; TSH term: 1.3 (0.6-2.4) mIU/L; TSH preterm: 1.1 (0.4-2) mIU/L; p< 0.0001).

The correlation between gestational age (GA) and plasma concentrations of TSH and T4 was significant for the AGA group (TSH vs GA: rho=0.036, p<0.001; T4 vs GA: rho=0.168, p<0.001). For the SGA group, it was only significant for T4 vs GA (rho=0.163, p<0.001; TSH vs GA: rho=0.016, p=0.656). Plasma concentrations of the two hormones increased with increasing gestational age at birth, but T4 concentrations of SGA newborns were constantly lower than those of AGA babies, and TSH concentrations were constantly higher, except in babies with the lowest gestational ages (Figs. 3, 4, 5)

Of the 14,092 babies screened, 139 (0.98%) were recalled for altered thyroid hormone concentrations, Only eight recalled babies were diagnosed with hypothyroidism and all were AGA.

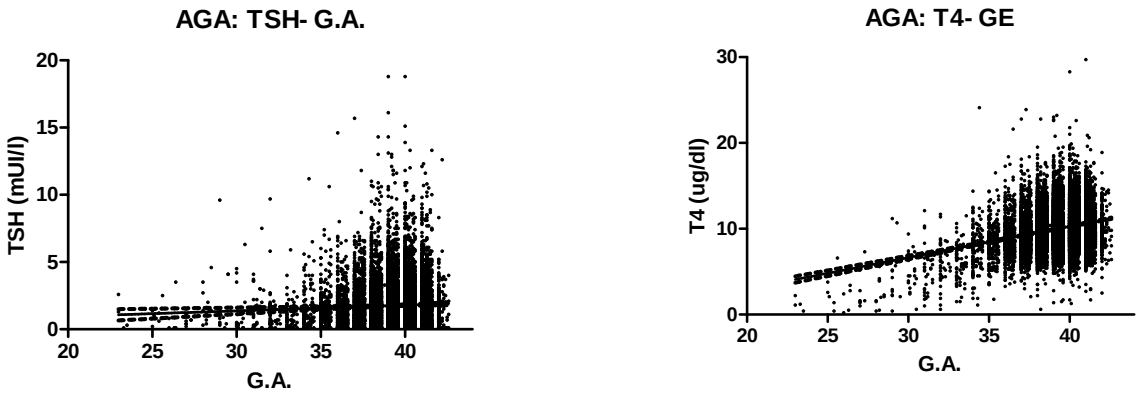
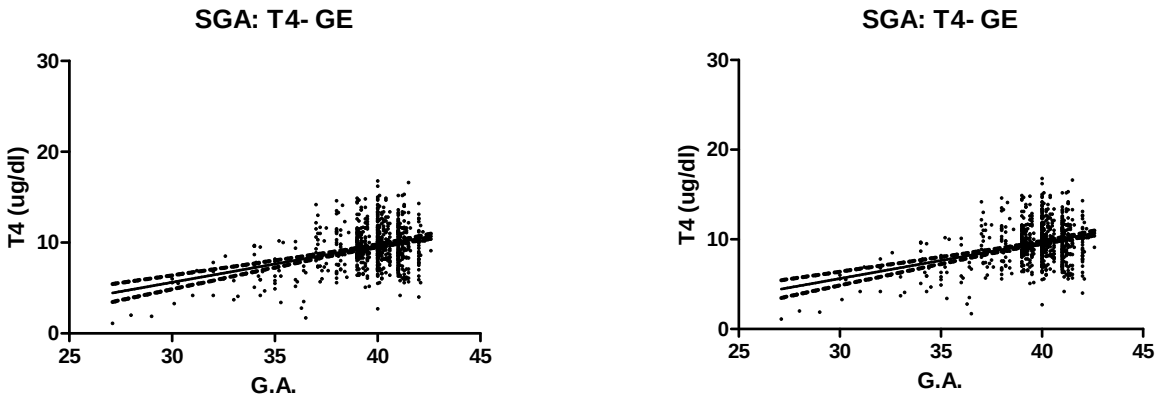



**Figure 3. Correlations between plasma concentrations of TSH and T4 in relation to gestational age (GA) in AGA newborns.**




**Figures 4. Correlations between plasma concentrations of TSH and T4 in relation to gestational age (GA) in SGA newborns.**

Although congenital hypothyroidism was not diagnosed in any SGA baby, this population showed double the incidence of TSH and T4 anomalies of the AGA babies. SGA newborns were mostly recalled for transient reduction in thyroxinemia (transient hypothyroxinemia) which returned to normal in the months that followed.

1.84% of SGA and 0.93% of AGA newborns. This different was statistically significant ($p<0.01$). The reasons for recall are indicated in Table 2.

No significant differences were observed between male and female babies or between SGA under the 3rd percentile and SGA below the 10th percentile.

**Table 2. Reasons for recall.**

| | TOTAL | AGA | SGA |
|---|---|---|---|
| **TSH ↑ and T4↓** | 5 | 5 (0.037%) | 0 |
| **TSH ↑** | 37 | 32 (0.24%) | 5 (0.65%) |
| **T4↓** | 97 | 88 (0.66%) | 9 (1.18%) |

However, the former showed lower concentrations of T4 and higher TSH than the latter (SGA < 3rd perc T4: 9.2 (7.5-10.9) ng/dL, TSH: 1.6 (0.7-2.6) mIU/L; SGA < 10th perc T4: 9.5 (8.2-11.2) ng/dL, TSH: 1.5 (0.6-2.8) mIU/L).

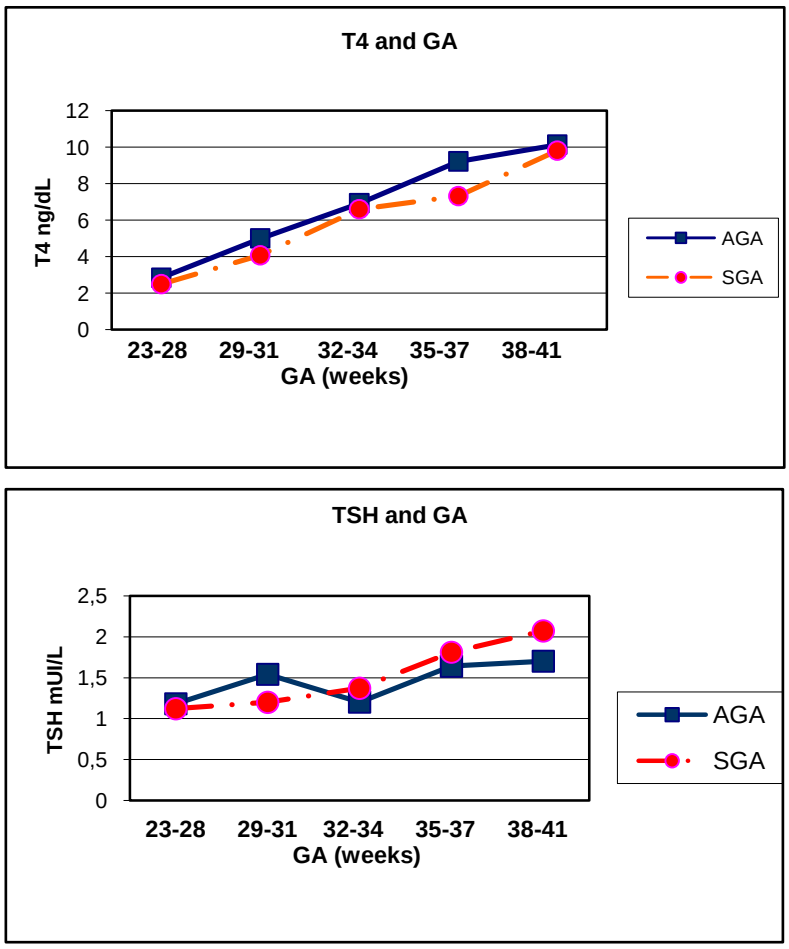



**Figure 5. Plasma concentrations of T4 and TSH in relation to GA in AGA and SGA newborns**

Comparison of plasma concentrations of thyroid hormone in a population of 71 AGA newborns of mothers undergoing thyroxine therapy (Eutirox) during pregnancy with those of AGA newborns of mothers not undergoing such treatment showed statistically significant differences in T4 secretion (babies of treated mothers T4: 9.2 (7.8-10.5) ng/dL; babies of untreated mothers T4: 9.8 (8.4-11.6) ng/dL; p=0.04) but not TSH concentrations (babies of treated mothers TSH: 1.35 (0.5-2.6) mIU/L; babies of untreated mothers TSH 1.3 (0.6-2.4) mIU/L; p=0.4).

**Discussion**

Various authors have observed that adults born small for gestational age are at higher risk of pathological events such as hypertension, insulin resistance, obesity, dyslipidemia, cardiovascular disease and stroke. Studies of SGA newborns have been extended to infancy and the role of hormones such as insulin, glucagon, cortisol, ACTH and GH have been studied in depth [3,19-25]. Due to its therapeutic implications, growth hormone is of particular interest.

The secretion of thyroid hormones in SGA subjects has been investigated to a lesser extent, especially in the neonatal period. To our knowledge, only six published studies have examined differences in secretion of thyroid hormones in AGA and SGA babies in the fetal period or the first week of life. One analyzed these hormones by cordocentesis in the fetal period, four in cord blood at birth and one in the first week of life and subsequent days [13-18] (Table 3).

Our results are in line with those of Setia et al. [14] in cord blood and those of Thorpe-Beeston et al. [13] who used cordocentesis, finding higher concentrations of TSH and lower concentrations of T4 in SGA newborns. Our results are in contrast with those of Nieto-Diaz et al. [17] and Brock Jacobsen et al. [15] as far as TSH concentrations are concerned. Rashimi et al. [16] and Mahajan et al. [18] did not find any significant differences in plasma concentrations of thyroid hormones at birth between SGA and AGA newborns.

**Table 3. Published studies on thyroid hormones in SGA newborns.**

| Study title | Authors Year | Population | Sampling period | AGA vs SGA results |
|---|---|---|---|---|
| Increased insulin sensitivity in intrauterine growth retarded newborns - Do thyroid hormones play a role? | Setia et al. 2006[14] | 50 IUGR vs 50 controls | At birth form cord | TSH ⇑ SGA (p=0.009) T4 ⇓SGA (p<0.001) |
| Thyroid function in small for gestational age fetuses | Thorpe-Beeston et al. 1991[13] | 49 SGA vs 62 AGA | Cordocentesis | TSH ⇑ SGA (p<0.001) T4 ⇓ SGA (p<0.01) |
| Endocrine regulation in asymmetric intrauterine fetal growth retardation | Mahajan et al. 2006[18] | 74 SGA vs 226 AGA | At birth from cord | TSH, T4 (p=ns) |
| Effect of perinatal factors on cord blood thyroid stimulating hormone levels | Rashimi et al. 2007[16] | 296 SGA vs 1294 AGA | At birth from cord | TSH (p=ns) |
| Intrauterine growth retardation at term: association between anthropometric and endocrine parameters | Nieto-Diaz et al. 1996[17] | 31 IUGR vs 45 controls | At birth from cord | TSH ⇓SGA (p<0.01) |
| Changes in serum concentrations of thyroid hormones and thyroid hormone-binding proteins during early infancy | Brock Jacobsen et al. 1979[15] | 91 SGA vs 127 AGA vs 88 preterm | 7th - 240th day of life | TSH not significant T4 ⇓ SGA (p<0.01) |

Since we assessed babies on the third day of life, our results should not be affected by confounding factors such as type of delivery, fetal distress and maternal diseases, all of which may affect TSH secretion at birth.

Since differences in TSH between AGA and SGA babies are relatively small and can only emerge in a large population, the population examined by Nieto-Diaz was presumably too small to detect statistically significant differences. Our data cannot be compared with that of Brock Jacobsen et al. who examined babies after the first week of life.

Our study considered newborns on the third day of life, when screening for congenital hypothyroidism was performed. Our finding of higher TSH and lower T4 in SGA newborns indicates reduced fetal secretion of T4 persisting in the first days after delivery. This reduced secretion could be due to retarded development of the gland, caused by the malnutrition typical of intrauterine growth retardation, and by any placental hypoxia.

Recent studies on populations of malnourished babies found T4 concentrations lower and TSH concentrations higher than in controls. Since fetal malnutrition is a typical aspect of intrauterine growth retardation, it seems likely that malnutrition has the same negative effects on the thyroid gland in the fetal period as in postnatal life. The same seems likely for SGA newborns, who are typically undernourished babies [26, 27]. We interpret the finding of high plasma concentrations of TSH in our population of SGA newborns as a correct pituitary response to low levels of T4 in the fetal and neonatal periods, suggesting that the pituitary is not influenced by nutritional status. Our recent research on VLBW babies in the first week of life showed that SGA babies have lower plasma concentrations of cortisol and higher ACTH than AGA newborns, again demonstrating correct pituitary function [28].

Our results showed significantly lower plasma concentrations of T4 and TSH in premature than in term babies. As already described in the literature, we too found a positive correlation between gestational

age and plasma concentrations of both thyroid hormones in AGA and of only T4 in SGA. However, SGA babies showed lower concentrations of T4 in relation to gestational age. The comparison of preterm AGA and preterm SGA babies revealed that T4 concentrations were significantly lower in the latter group, whereas no significant differences in TSH concentrations were found, probably due to the smaller population considered. This finding demonstrates that intrauterine growth retardation determines reduced thyroid maturation, and consequently also reduced secretion of T4, also at lower gestational ages, and this probably occurs simultaneously with onset of the pathology that delays fetal growth.

Out of 14,092 babies screened, 139 (0.98%) were recalled: 1.84% of SGA versus 0.93% of AGA babies. A SGA newborn therefore has a much higher probability of positivity in the screening test for congenital hypothyroidism. We found a higher incidence of alterations in plasma concentrations of T4 and TSH in SGA than AGA newborns, however all babies who had altered levels of both hormones and were diagnosed with hypothyroidism belonged to the AGA group. Hypothyroxinemia found in SGA newborns was transient and disappeared by the next follow-up.

One hypothesis for why SGA babies have low plasma concentrations of T4 in utero and in the first days of life could be a deficiency of phenylalanine and tyrosine caused by the direct effect of malnutrition on synthesis of thyroid hormones. This endocrine and metabolic state could be an advantage in conditions of poor nutrition or pathologies leading to growth retardation, because it is associated with reduced oxygen consumption. The fact that no SGA newborn had hypothyroidism and that hypothyroxinemia normalized spontaneously in the first months of life, suggests that adequate nutrition leads to recovery of thyroid function.

**Conclusion**

In SGA newborns, particularly if preterm, transient hypothyroxinemia occurs. Term SGA newborns have lower plasma concentrations of thyroxine than term AGA babies, whereas their concentrations of TSH are higher than those of AGA newborns, suggesting that SGA have correct pituitary function. The changes observed in SGA babies in the third day of life tend to disappear in time, demonstrating recovery of thyroid function. However, it seems worthwhile enrolling these babies in follow-up protocols to monitor correct gland function, certainly in the first year of life and possibly in subsequent periods as well.

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