SHORT COMMUNICATION

TRIIODOTHYRONINE CONCENTRATION IN CORD AND MATERNAL SERA AT TERM

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SUMMARY

1. Specific radioimmunoassays have been employed to measure triiodothyronine (T₃) and thyroxine (T₄) concentrations in the cord serum of fifty-five healthy babies and in a second series of fifteen paired cord and maternal blood samples.

2. The mean cord serum T₃ was 332±136 (SD) pg/ml. In the paired series the mean cord serum T₃ was 355±142 pg/ml whereas the mean maternal value was 1557±283 pg/ml.

3. Serum thyrotrophin (TSH) concentration was raised in cord serum compared with maternal serum.

Key words: thyroid hormones, neonates.

The human foetal hypothalamic pituitary thyroid axis is operational early in gestation and thence functions independently of the maternal system (Fisher, Hobel, Garza & Pierce, 1970). Serum thyroxine (T₄) and protein-bound iodine (PBI) levels increase progressively with gestational age and birthweight (Fisher et al., 1970; Perry, Hodgman & Starr, 1965). At term, serum total T₄ and PBI levels are similar in maternal and cord blood, albeit at a higher level than normal (Fisher, Odell, Hobel & Garza, 1969; Robin, Refetoff, Fang & Selenkov, 1969), but serum free T₄ concentrations are significantly higher in the foetus, presumably owing to a greater degree of saturation of thyroid-binding proteins (Perry et al., 1965). The rise in foetal serum T₄ concentration during gestation, in the absence of any demonstrable placental transfer of T₄, suggests that there is a progressive rise of the T₄ production rate in response to persistent hypersecretion of pituitary thyrotrophin (TSH) (Fisher et al., 1970). Despite the high circulating serum T₄ level there is a further increase in serum TSH soon after delivery (Fisher & Odell, 1969). To date, relatively little information has emerged concerning the role of triiodothyronine (T₃) secretion in the control of pituitary thyroid function in the foetus at term. This communication reports the results of determination of serum T₃, T₄ and TSH levels in maternal and foetal blood at birth.

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MATERIALS AND METHODS

T₃ concentrations were measured in 0.05 ml samples of whole serum by a sensitive, specific radioimmunoassay technique employing 8-anilino-1-naphthalene sulphonic acid (ANS) to inhibit T₃ binding to thyroxine-binding globulin (TBG). Assay incubation mixtures comprised 100 µl of appropriately diluted antiserum (usually 1:50000, 100 µg of ANS), 30 pg of ¹²⁵I-labelled T₃, 50 µl of serum (either the test sample or charcoal-stripped serum in the case of standards), and 100 µl of standard dilutions of T₃ or an equivalent volume of buffer as appropriate, the incubation sample being made up to 1 ml with buffer [barbitone 0.05 M containing thiomersal (0.1 g/l) and bovine serum albumin (BSA, 0.5 g/l)]. Separation of bound and free fractions was effected by using 50 µl of a suspension of charcoal (Norit OL) in methyl cellulose–barbitone buffer to adsorb the free material. Under the assay conditions employed, the detection limit of the system is of the order of 50 pg of T₃/ml of serum, and no demonstrable effects arise from cross-reaction of T₄ with the T₃ antiserum. By using this procedure the normal range for serum T₃ concentrations in healthy euthyroid subjects has been defined as 850–1600 pg/ml, which is essentially identical with the range yielded by the more elaborate radioimmunoassay technique of Brown, Ekins, Ellis & Williams (1970).

Serum total T₄ was measured by using an analogous method relying on a specific T₄ antiserum and ANS to block the binding of T₄ to serum proteins in the incubation mixture. Except for the volume of serum used (10 µl), and the amount of ANS employed to inhibit T₄ protein binding, the experimental details of the assay procedure are essentially identical with those relating to the T₃ assay. Serum T₄ levels measured by this technique are similar to those obtained with the conventional protein-binding methods previously reported (Ekins, 1960; Ekins, Ellis & Williams, 1969). The normal range for serum T₄ concentrations by all methods approximates to 45–115 ng/ml.

Specific antisera for both these assays were prepared in this laboratory by using modified techniques (C. J. Eastman, J. M. Corocan, A. Jequier, R. P. Ekins & E. S. Williams, unpublished work) of those employed by Brown, Ekins, Ellis & Reith (1970).

The degree of saturation of thyroid-binding proteins was estimated by the Thyopac 3 method (Amersham). The free thyroxine index was derived by conventional methods.

Serum TSH concentration was measured by a modification of the double-antibody radioimmunoassay method of Raud & Odell (1969). Antiserum to human TSH and human TSH for labelling was a gift of the Hormone Distribution Programme of the National Pituitary Agency. Results are expressed in µunits/ml of the MRC Research Standard 68/38. HCG (Organon) 10 i.u. was added to each assay tube in both maternal and neonatal samples.

Cord blood samples were obtained from the umbilical veins of fifty-five healthy babies within minutes of delivery. The period of gestation varied from 32 to 40 weeks, but most were full term. A second series of fifteen paired cord and maternal blood samples were obtained for comparison of serum T₃, T₄ and TSH concentrations.

RESULTS

In the fifty-five cord sera, T₃ levels ranged from 100 to 750 pg/ml with a mean level of 332 ± 136 pg/ml (SD). These levels are below the normal range of healthy euthyroid adults and prepubertal children. Indeed, the range and mean serum T₃ level are similar to the results we have
found in clinically overt hypothyroid patients. The results of serum \( T_3 \) and \( T_4 \) determination on the fifteen paired cord and maternal sera are shown in Fig. 1. The mean serum \( T_3 \) concentration in cord sera of \( 355 \pm 142 \) pg/ml was significantly different \( (P<0.001) \) from the mean serum \( T_3 \) in maternal sera of \( 1557 \pm 283 \) pg/ml. The range and mean serum \( T_4 \) levels were slightly decreased in cord sera as compared with maternal sera (cord sera \( 86 \pm 11 \) ng/ml, maternal sera \( 93 \pm 13 \) ng/ml). However, determinations of the free thyroxine index in five paired sera revealed a higher mean value in cord sera, but this was not statistically significant. Serum TSH levels were increased in cord sera, range \( 5.6-35.0 \) \( \mu \)units/ml with a mean of \( 15.9 \), in contrast with maternal levels, which ranged from 2.5 to 6.0 \( \mu \)units/ml with a mean of 4.1.

![Scatter diagram of serum \( T_3 \) and \( T_4 \) concentrations in maternal and cord blood (mean values shown by horizontal bars).](image)

**DISCUSSION**

The significant lowering in foetal serum \( T_3 \) concentration observed in this study contrasts with the slightly increased maternal serum \( T_3 \) concentration, and also with the closer correspondence in \( T_4 \) concentrations between cord and maternal sera. This finding is at variance with
previous reports of normal or increased serum T₃ levels in cord blood (Dussault, Row, Lickrish & Volpe, 1969; Hotelling & Sherwood, 1971) notwithstanding the increased maternal/cord serum T₃ ratio observed by the latter workers. Our own findings are in essential agreement with the recent observations of Larsen (1972) of low serum T₃ levels (mean 0.53 ng/ml) in eight cord sera, although they demonstrate a greater and more consistent decrease than those reported by Larsen, some of whose cord serum values fell within the euthyroid range. The results of Dussault et al. (1969) and Hotelling & Sherwood (1971) were obtained by using two different protein-binding assay methods both of which are now believed to have been liable to artifactual overestimation of the serum T₃ concentration, in contrast with the specific sensitive radioimmunoassay technique used in the present work. However, Montalvo, Wahner, Mayberry & Lum (1972) by using a protein-binding technique, have also reported cord serum T₃ values (0.805±0.019 ng/ml, SD) falling within their hypothyroid range, notwithstanding the higher absolute levels observed both in maternal (2.65±0.43 ng/ml) and cord sera by using this method.

It is clear that continuing disparities in estimates of circulating T₃ yielded by different assay methods have tended to obscure the divergence between maternal and cord serum values that the studies reported here appear to confirm. Our own serum total and free T₄ and serum TSH determinations are in agreement with results reported by other workers (Fisher et al., 1970; Robin et al., 1969). Our observed serum T₃ values in normal subjects also show good agreement with those of Larsen (1972); moreover they confirm the radioimmunoassay results originally reported from this laboratory by using a well-validated extraction method (Brown et al., 1971).

The mechanism of the low circulating T₃ level in the foetus or the physiological significance of this finding in foetal development is not clear. The ability of the thyroid to respond to TSH stimulation is well demonstrated by the high foetal serum T₄ concentration. During extra-uterine life the thyroid secretes both T₃ and T₄, and in response to intensive TSH stimulation may even release T₃ in preference to T₄. In addition to thyroidal secretion, T₃ is formed in vivo by peripheral monodeiodination of T₄, which appears to be the predominant source of T₃ production in the adult. Although we have no results on conversion of T₄ into T₃ in utero it is possible to speculate that immaturity or suppression of the conversion mechanism in the foetus leads to diminished T₃ peripheral production and an increased turnover of thyroidal T₃. This hypothesis, which could account for the low serum T₃ concentrations observed, is worth investigation.

The low serum T₃ levels in the foetus may explain the persistent hypersecretion of TSH that is not suppressed by increased serum total and free T₄ concentration. Specific T₃ binding sites in the anterior pituitary have recently been reported (Shadlow, Surks, Schwartz & Oppenheimer, 1972) and it is possible that T₃ exerts its negative feedback effect on TSH release via these sites.

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REFERENCES


