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Thyroid Function in Anemic Fetuses

J. Guy Thorpe-Beeston[a], *Kypros H. Nicolaides*[a], *Rosalinde J.M. Snijders*[a], *Carl V. Felton*[b]

[a] Harris Birthright Research Centre for Fetal Medicine, Department of Obstetrics and Gynaecology, King's College School of Medicine and Dentistry, and
[b] Wynn Institute for Metabolic Research, London, UK

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Abstract. Thyroid function was studied in 75 fetal blood samples obtained by cordocentesis from red cell isoimmunized pregnancies at 18–37 weeks of gestation. Thyroid-stimulating hormone (TSH), and free and total thyroxine and triiodothyronine were significantly higher than in normal controls. Furthermore, there was a significant association between the increase in TSH and the degree of fetal anemia.

Introduction

In normal fetuses, thyroid-stimulating hormone (TSH) and thyroid hormones increase with gestation. Furthermore, fetal TSH is higher and thyroid hormones are lower than adult values. These findings suggested that maturation of the fetal thyroid gland was independent of the pituitary, and that the fetal pituitary was not susceptible to negative feedback from the thyroid hormones [1].

In hypoxemic fetuses with intrauterine growth retardation (IUGR), fetal TSH is higher and thyroid hormones lower than in normal fetuses [2]. The decrease in thyroid hormones was thought to be a consequence of reduced supply of nutrients and oxygen due to uteroplacental insufficiency and/or reduced perfusion of the thyroid gland. Nevertheless, in uteroplacental insufficiency the decrease in thyroid hormones could have a beneficial effect by slowing metabolism and thereby reducing utilization of oxygen and nutrients. The increase in fetal TSH was either due to the decrease in thyroid hormones or rather the independent consequence of increased concentration of hypoxia-related hormones, such as noradrenaline [3], or increased brain perfusion, which is well documented in fetal hypoxemia [4, 5].

The aim of the present study was to examine fetal thyroid function in red cell isoimmunized pregnancies, which provide an alternative model of fetal hypoxemia; fetal blood gases are normal but, because of the

anemia, oxygen content is reduced [6]. In both red cell isoimmunization and uteroplacental insufficiency, fetal blood oxygen content is reduced, and noradrenaline and brain perfusion are increased [3–9]. However, unlike uteroplacental insufficiency, in red cell isoimmunization placental perfusion and therefore nutrient delivery from mother to fetus is normal. Furthermore, the fetal circulation is hyperdynamic and there is no redistribution at the expense of the viscera.

Patients and Methods

TSH, total thyroxine (T4), free thyroxine (FT4), total triiodothyronine (T3) and free triiodothyronine (FT3) were measured in 75 umbilical venous blood samples (1–2 ml) obtained by cordocentesis from 39 red cell isoimmunized pregnancies of 19–37 weeks of gestation. Gestational age was established by Naegeles' rule and confirmed by ultrasonographic examination in early pregnancy. Informed consent was obtained from the mothers and the project was approved by the hospital ethical committee.

Cordocentesis was performed as an outpatient procedure, without maternal sedation or fetal paralysis [10]. The pre-transfusion fetal hemoglobin concentration was measured (Coulter Channelizer, Porter Electronics Ltd., Luton, UK) and, if this was below the 5th percentile for gestation, fresh packed blood compatible with that of the mother was transfused as necessary to correct the fetal anemia. In this study only pre-transfusion samples were analyzed. In 29 cases, the fetal blood samples were obtained from previously untransfused fetuses and Kleihauer testing demonstrated that the samples contained only fetal erythrocytes. In 46 cases the fetuses had received blood transfusions 2–3 weeks previously and all erythrocytes in the fetal circulation were adult.

Fetal blood samples were collected into plain tubes, centrifuged for 10 min at 2,000 rpm and the serum collected and stored at −20 °C. Serum TSH was measured by immunoradiometric assay (Celltech Diagnostics, Slough, UK) and thyroid hormones were measured using solid-phase radioimmunoassays (Diagnostic Products Corporation, Los Angeles, Calif., USA). The inter-assay and intra-assay coefficients of variation for the TSH, T4-binding globulin, total T4 and FT4, and total T3 and FT3 were: 4.5 and 3.9%, 4.5 and 3.4%, 4.9 and 4.1%, 6.5 and 4.4%, 6.6 and 5.4%, and 4.8 and 4.5%, respectively.

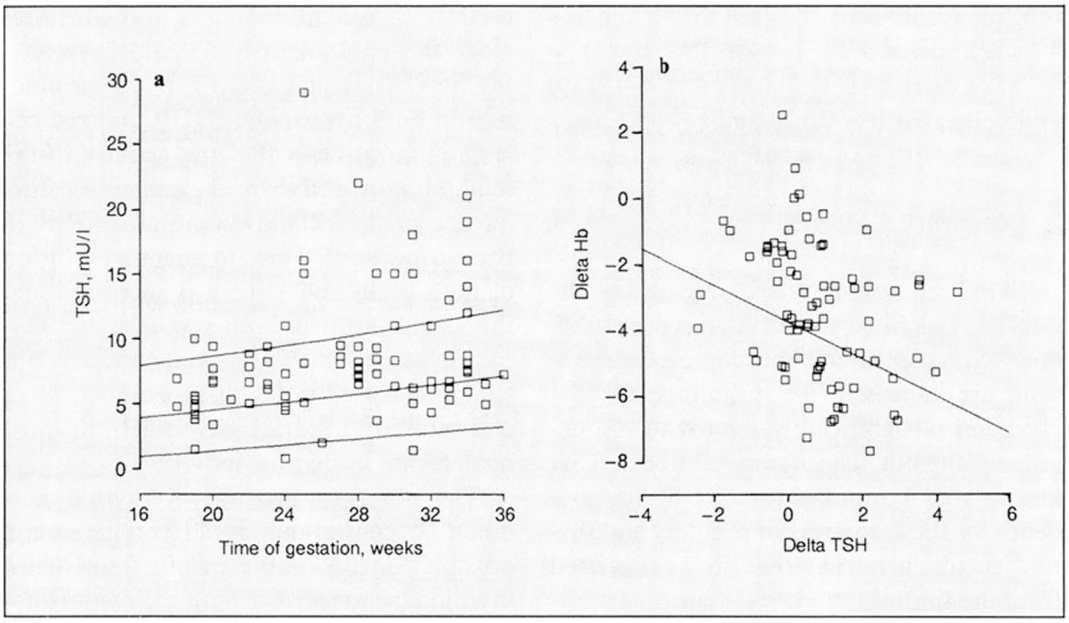
Statistical Analysis

Since in normal pregnancies, fetal TSH, thyroid hormone concentrations [1] and hemoglobin concentration [11] change with gestational age, the individual values from the red cell isoimmunized pregnancies were expressed as the number of standard deviations (SD) by which they differed from the respective normal mean for gestation (delta values). Student's t test was used to determine the significance of any difference in the mean values of the measured variables between the red cell isoimmunized pregnancies and the previously published values for normal controls. Regression analysis was used to determine whether there were any significant associations between delta TSH, delta thyroid hormones and the degree of fetal anemia (delta hemoglobin).

Results

In red cell isoimmunized pregnancies, compared to the normal controls, the mean fetal hemoglobin concentration was lower (mean difference = − 1.76 SD, $t = -8.09$, $p < 0.0001$), and the mean TSH (fig. 1; mean difference = 0.984, $t = 4.86$, $p < 0.0001$), T4 (mean difference = 0.399, $t = 2.02$, $p < 0.05$). FT4 (fig. 2; mean difference = 0.705, $t = 2.84$, $p < 0.01$), T3 (mean difference = 0.329, $t = 2.55$, $p < 0.05$), FT3 (fig. 2; mean difference = 0.823, $t = 3.12$, $p < 0.01$) were significantly higher.

Delta TSH was significantly associated with delta hemoglobin (fig. 1; $r = -0.323$, $n = 75$, $p < 0.01$); multiple regression analysis demonstrated that this association was independent of whether the origin of erythrocytes in fetal blood was fetal or adult ($t = 0.04$, $p = 0.972$). There were no significant associations between delta TSH or delta he-



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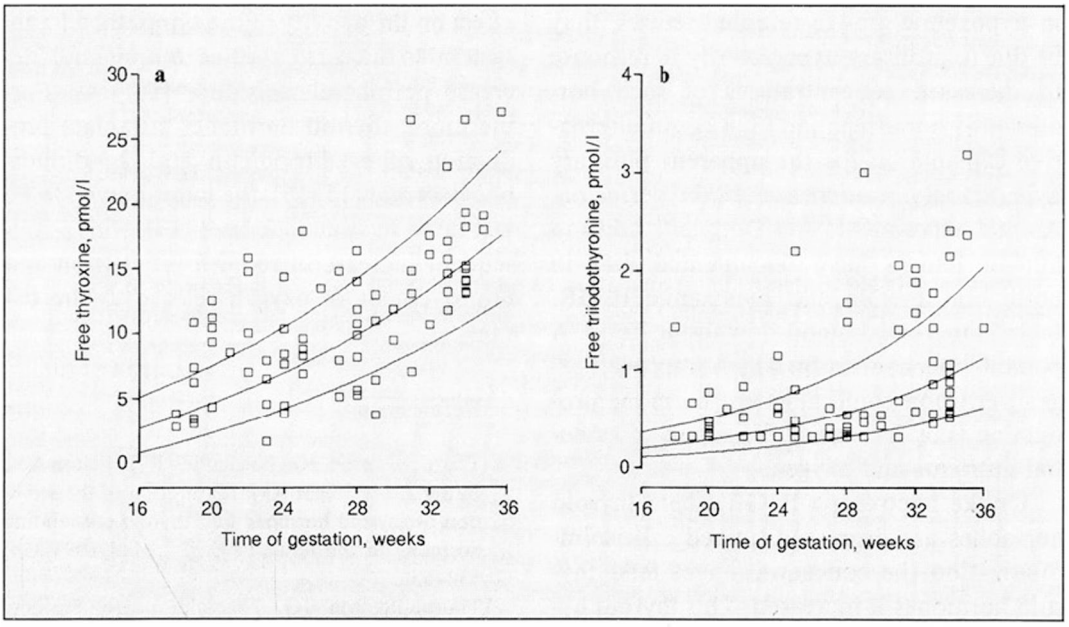

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Fig. 1. a Fetal thyroid-stimulating hormone (TSH) in red cell isoimmunized pregnancies (□) plotted on the reference range (mean, 5th and 95th percentiles) [1] for gestation. **b** Relation of fetal delta TSH and delta hemoglobin ($r = -0.323$, $n = 75$, $p < 0.01$).

Fig. 2. Fetal free thyroxine (**a**) and triiodothyronine (**b**) in red cell isoimmunized pregnancies (□) plotted on the appropriate reference range (mean, 5th and 95th percentiles) [1] for gestation.

moglobin and delta T4 ($r = 0.121$ and $r = -0.152$), delta FT4 ($r = 0.153$ and $r = -0.132$), delta T3 ($r = -0.031$ and $r = -0.139$) and delta FT3 ($r = 0.126$ and $r = -0.126$).

Comment

In red cell isoimmunized pregnancies, the fetal hemoglobin concentration is decreased, and TSH and thyroid hormone concentrations are increased; the magnitude of TSH elevation is significantly related to the degree of anemia. The increase in both TSH and thyroid hormones provide further evidence for the autonomy of pituitary and thyroid glands in intrauterine life as suggested from the findings in normal fetuses [1].

The increased TSH in anemic fetuses, as in hypoxemic growth-retarded fetuses, may be due to pituitary hyperactivity in response to increased concentrations of such hormones as noradrenaline [3, 12]. An alternative explanation for the apparent pituitary hyperactivity is increased brain perfusion. Animal experiments and Doppler studies in human fetuses have documented that in both fetal anemia and hypoxemic IUGR, there is increased blood flow to the brain. A possible mechanism by which improved organ perfusion could augment hormone production is by increasing the supply of essential nutrients and oxygen.

Unlike hypoxemic IUGR where thyroid hormones are decreased, in red cell isoimmunization the concentration of fetal thyroid hormones is increased. This thyroid hyperactivity may be due to the increased level of TSH. However, there was no significant association between delta TSH and delta thyroid hormones. Furthermore, despite the already high TSH concentrations, the low levels of thyroid hormones in normal fetuses make this an unlikely explanation. A unifying hypothesis that could explain the findings in both hypoxemic IUGR and red cell isoimmunization is that the activity of the fetal pituitary and thyroid glands is a consequence of the hemodynamic alterations in these conditions. Thus, in anemia perfusion of both brain and viscera is increased and this could result in both pituitary and thyroid hyperactivity. In hypoxia, brain perfusion is increased at the expense of the viscera and pituitary hyperactivity is accompanied by decrease in thyroid activity.

The observed increase in thyroid hormone concentration, would confer several possible benefits on the anemic fetus. Thus, thyroid hormones have both a direct cardiotonic effect and also a possible synergistic effect on the activity of the sympathoadrenal system to increase cardiac output and decrease peripheral resistance [13, 14]. Furthermore, thyroid hormones stimulate production of erythropoietin and 2,3-diphosphoglycerate [15, 16], the latter known to be increased in anemic fetuses [17], with a consequent increase in red cell production and improvement in oxygen release to the tissues.

References

1 Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM: Maturation of the secretion of thyroid hormone and thyroid stimulating hormone in the fetus. N Engl J Med 1991;324: 532–536.

2 Thorpe-Beeston JG, Nicolaides KH, Snijders RJM, Felton CV, McGregor AM: Thyroid function in small for gestational age fetuses. Obstet Gynecol 1991;77:701–706.

3 Greenough A, Nicolaides KH, Lagercrantz H: Human fetal sympathoadrenal responsiveness. Early Hum Dev 1990;23:9–13.

4 Bilardo CM, Nicolaides KH, Campbell S: Doppler measurements of fetal and uteroplacental circulations: Relationship with umbilical venous blood gases measured at cordocentesis. Am J Obstet Gynecol 1990;161:115–120.
5 Vyas S, Nicolaides KH, Bower S, Campbell S: Middle cerebral artery flow velocity waveforms in fetal hypoxemia. Br J Obstet Gynaecol 1990;97: 797–803.
6 Nicolaides KH: Studies on fetal physiology and pathophysiology in rhesus disease. Semin Perinatol 1989;13:328–337.
7 Nicolaides KH, Bilardo CM, Campbell S: Prediction of fetal anaemia by measurement of the mean blood velocity in the fetal aorta. Am J Obstet Gynecol 1990;162:209–214.
8 Vyas S, Nicolaides KH, Campbell S: Doppler examination of the middle cerebral artery in anemic fetuses. Am J Obstet Gynecol 1990;162:1066–1068.
9 Nicolaides KH, Economides DL, Soothill PW: Blood gases, pH and lactate in appropriate- and small-for-gestational age fetuses. Am J Obstet Gynecol 1989;161:996–1001.
10 Nicolaides KH, Soothill PW, Rodeck CH, Clewell W: Rh Disease: Intravascular fetal blood transfusion by cordocentesis. Fetal Ther 1986;1:185–192.
11 Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH: Fetal haemoglobin measurements in the assessment of red cell isoimmunisation. Lancet 1988;i:1073–1075.
12 Fukuda S: Correlation between function of the pituitary-thyroid axis and metabolism of catecholamines by the fetus at delivery. Clin Endocrinol 1987;27:331–338.
13 Grossman W, Robin NI, Johnson LW, et al: The enhanced myocardial contractility of thyrotoxicosis: Role of the beta adrenergic receptor. Ann Intern Med 1971;74:869–874.
14 Degroot WJ, Leonard JJ: Hyperthyroidism as a high cardiac output state. Am Heart J 1970;79: 265–275.
15 Das KS, Mukherjee M, Sarkar TK, et al: Erythropoiesis and erythropoietin in hypo- and hyperthyroidism. J Clin Endocrinol Metab 1975;40:211–220.
16 Synder LM, Reddy W: Thyroid hormone control of erythrocyte 2,3-diphosphoglyceric acid concentrations. Science 1970;169:879–880.
17 Soothill PW, Lestas AN, Nicolaides KH, Rodeck CH, Bellingham AJ: 2,3-Diphosphoglycerate in normal, anaemic and transfused human fetuses. Clin Sci 1988;74:527–530.

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Dr. K.H. Nicolaides
Harris Birthright Research Center for
Fetal Medicine
Department of Obstetrics and Gynaecology
King's College School of Medicine and Dentistry
Denmark Hill
London SE5 8RX (UK)