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Relations between the fetal circulation and pituitary-thyroid function

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Abstract

Objective—To study the relation between changes in the fetal thyroid hormone and thyroid stimulating hormone (TSH) concentrations and alterations in the fetal circulation as assessed by Doppler ultrasound.
Design—A cross-sectional study of small for gestational age (SGA) and red-cell isoimmunized fetuses undergoing cordocentesis and Doppler studies for the assessment and determination of fetal karyotype, acid-base balance and haemoglobin concentration.
Setting—Harris Birthright Research Centre for Fetal Medicine, King's College, London.
Subjects—38 growth retarded and 38 red-cell isoimmunised fetuses.
Interventions—Cordocentesis.
Main outcome measures—Serum TSH total and free thyroxine (T4, FT4) and total and free triiodothyronine (T3, FT3) concentrations; middle cerebral artery (MCAVm) and descending thoracic aorta (AoVm) mean blood velocities; fetal Po_2 and haemoglobin concentration (Hb).
Results—Delta values (δ) calculated as the number of SDs from the respective normal mean for gestation were used to compare the results with those from a previous study of normal fetuses. Mean AoVm was increased in the isoimmunized fetuses ($P<0{\cdot}001$) but decreased in the SGA fetuses ($P<0{\cdot}001$). Mean MCAVm was increased in both groups ($P<0{\cdot}01$; $P<0{\cdot}001$). There were significant associations between the gestational age adjusted values for TSH and MCAVm ($r = 0{\cdot}23$, $P<0{\cdot}05$) and between T4, FT4 or FT3 and AoVm ($r = 0{\cdot}41$, $P<0{\cdot}01$; $r = 0{\cdot}50$, $P<0{\cdot}001$; $r = 0{\cdot}36$, $P<0{\cdot}01$ respectively). In addition, T4 and FT4 were associated with δPo_2 and δHb.
Conclusion—In the hypoxaemic hypoxia of growth retardation and the anaemic hypoxia of rhesus disease there are significant associations between changes in fetal thyroid hormone concentrations and changes in fetal blood flow as assessed by Doppler. Irrespective of whether altered blood flow is the cause or effect of changes in thyroid hormone concentrations, the observed changes could have beneficial effects for fetal survival, in the presence of a hostile intrauterine environment.

In normal fetuses, there is an autonomous increase in thyroid stimulating hormone (TSH) and thyroid hormones with gestation (Thorpe-Beeston *et al.* 1991a). In hypoxaemic growth-

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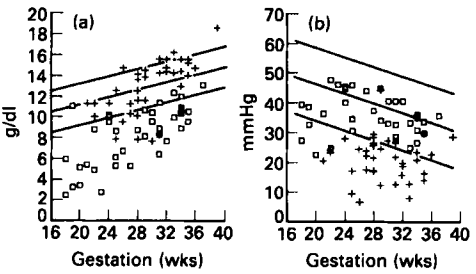

Fig. 1. Haemoglobin concentration (a) and Po_2 (b) of the small for gestational age (+) and rhesus affected (□) fetuses plotted on the appropriate reference range (mean, 5th and 95th centile) for gestation.

retarded fetuses, TSH is higher and thyroid hormones lower than in normal fetuses (Thorpe-Beeston *et al.* 1991b). In rhesus affected anaemic fetuses both the TSH and thyroid hormone concentrations are increased (Thorpe-Beeston *et al.* 1991c). A unifying hypothesis, that could explain the findings in both hypoxaemic growth retardation and red cell isoimmunization, is that the activity of the fetal pituitary and thyroid glands is a consequence of the haemodynamic alterations in these conditions. Thus in anaemia, perfusion of both brain and viscera is increased (Vyas *et al.* 1990; Nicolaides *et al.* 1990) and this could result in both pituitary and thyroid hyperactivity. In hypoxia, brain perfusion is increased at the expense of the viscera (Bilardo *et al.* 1990) and this could be the cause of pituitary hyperactivity and the decrease in thyroid activity.

The aim of the present study was to test this hypothesis by investigating the relation between changes in the thyroid hormone and TSH concentrations and alterations in the fetal circulation as assessed by Doppler ultrasound.

Subjects and methods

In this cross-sectional study, Doppler ultrasonographic studies were performed within 30–60 min before cordocentesis in 38 small-for-gestational age (SGA) and 38 rhesus affected fetuses at 18–39 weeks gestation. In the SGA group, the fetal abdominal circumference was below the 2·5th centile of our normal range and cordocentesis was performed for fetal karyotyping and blood gas analysis (Nicolaides *et al.* 1989a). All fetuses were chromosomally and morphologically normal and growth retardation was confirmed at delivery when the birthweight was below the 5th centile for gestation and sex (Yudkin *et al.* 1987). In the rhesus affected group, cordocentesis was performed for determination of fetal haemoglobin and intravascular blood transfusion as necessary (Nicolaides *et al.* 1986a).

Flow velocity waveforms were recorded from the fetal descending thoracic aorta (Ao) and the middle cerebral arteries (MCA), using pulsed Doppler ultrasonography after vessel identification by colour flow imaging (Acuson 128, Mountain View, CA, USA). The Doppler sonograms were considered for measurements when there were no fetal gross body or chest movements and the fetal heart rate was between 120 and 140 beats/min. The high-pass filter was set at 150 Hz. The time-averaged intensity-weighted mean blood velocity (Vm) was calculated as described previously (Nicolaides *et al.* 1990; Vyas *et al.* 1990; Bilardo *et al.* 1990). The intra-observer coefficients of variation for AoVm and MCAVm are 6% and 11·1% respectively (Bilardo *et al* 1988; Vyas *et al.* 1990).

Cordocentesis was performed as an outpatient procedure without fetal or maternal sedation (Nicolaides *et al.* 1986b). The umbilical vein Po_2 (Radiometer ABL 330 blood gas analyser, Copenhagen, Denmark) and the fetal haemoglobin concentration (Coulter Channelizer, Porter Electronics Ltd., Luton, UK) were measured. Fetal blood (1–2 ml) was collected into plain tubes, centrifuged for 10 min at 2000 rpm, and the serum was stored at −20°C. TSH was measured by immunoradiometric assay (Celltech Diagnostics, Slough, UK) and total thyroxine (T4), free thyroxine (FT4), total triiodothyronine (T3) and free triiodothyronine (FT3) thyroid hormones were measured using solid-phase radioimmunoassays (Diagnostic Product Corporation, CA). The intra-assay

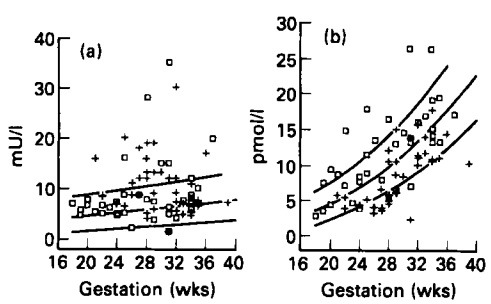

Fig. 2. Thyroid stimulating hormone (a) and free thyroxine (b) concentrations of the small for gestational age (+) and rhesus affected (□) fetuses plotted on the appropriate reference range (mean, 5th and 95th centile) for gestation.

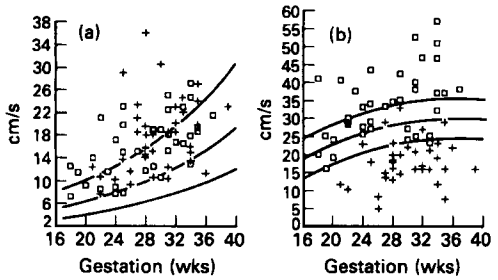

Fig. 3. Middle cerebral artery (a) and descending thoracic aorta (b) mean blood velocity of the small for gestational age (+) and rhesus affected (□) fetuses plotted on the appropriate reference range (mean, 5th and 95th centile) for gestation.

coefficient of variation for all assays was less than 6%.

Statistical analysis

Since in normal pregnancies, fetal TSH, thyroid hormone concentrations and Doppler variables change with gestation, in this study the values obtained from each fetus were expressed as the number of standard deviations (SDs) by which they differed from the respective normal mean for gestation (delta values = δ). Student's *t*-test was used to determine the significance of any difference in the mean values of the measured variables between the rhesus affected and the SGA fetuses and the values for normal controls as published by Thorpe-Beeston *et al.* (1991a). Regression analysis was used to determine if there were any significant associations between δ TSH, δ thyroid hormones, δ AoVm and δ MCAVm.

Results

The Doppler results and umbilical vein blood Po_2, haemoglobin, TSH and FT4 concentrations of the SGA and rhesus affected fetuses are plotted on the appropriate reference ranges for gestation in Figs. 1–3.

Compared with the appropriate normal means for gestation, the red cell isoimmunized pregnancies had (i) higher mean fetal concentrations of TSH, T4, FT4 and FT3 (TSH: mean difference = 0·85 SDs, $t = 3·06$, $P<0·01$; T4: mean difference = 0·54 SDs, $t = 2·17$, $P<0·05$; FT4: mean difference = 0·73 SDs, $t = 2·32$, $P<0·05$; FT3: mean difference = 0·97 SDs, $t = 2·65$, $P<0·01$) but a similar T3 concentration (mean difference = 0·12 SDs, $t = 0·65$); (ii) a lower mean haemoglobin concentration (mean difference = −2·95 SDs, $t = -7·6$, $P<0·0001$) but a similar Po_2 concentration (mean difference = −0·22 SDs, $t = 1·7$; and (iii) higher values for both mean AoVm and mean MCAVm (AoVm: mean difference = 1·62 SDs, $t = 4·06$, $P<0·001$; MCAVm: mean difference = 1·10 SDs, $t = 3·17$, $P<0·01$).

Compared with the appropriate normal mean for gestation, the SGA fetuses had (i) a higher mean TSH concentration and lower concentrations of both mean T4 and mean FT4 (TSH: mean difference = 1·29 SDs, $t = 4·91$, $P<0·0001$; T4: mean difference = 0·94 SDs, $t = 3·44$, $P<0·01$; FT4: mean difference = 1·36 SDs, $t = 5·34$, $P<0·001$) whereas the mean FT3 and mean T3 concentrations were not significantly different (FT3: mean difference = 0·34 SDs, $t = -1·17$; T3: mean difference = −0.10 SDs, $t = -0·37$), (ii) a lower mean fetal Po_2 concentration, but a similar mean haemoglobin concentration (Po_2: mean difference = 2·35 SDs, $t = -9·02$, $P<0·0001$); Hb: mean difference = 0·17 SDs, $t = 0·44$), and (iii) a lower mean AoVm and a higher mean MCAVm (AoVm: mean difference = −3·11 SDs, $t = -11·37$, $P<0·0001$; MCAVm: mean difference = 1·47 SDs, $t = 6·22$, $P<0·0001$).

The associations between delta (δ) values for fetal TSH, thyroid hormones and Po_2, haemoglobin and Doppler variables are shown in Table 1. Fetal TSH was significantly associated with δ MCAVm. Fetal T4, FT4 and FT3 were significantly associated with δ AoVm. In addition, T4 and FT4 were associated with δ Po_2 and δ Hb.

Multiple regression analysis demonstrated the

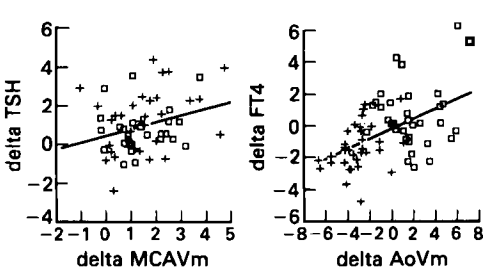

Fig. 4. Relation of delta values in small for gestational age (+) and rhesus affected (□) fetuses (in SDs from the appropriate mean for gestation) for fetal thyroid stimulating hormone (TSH) and free thyroxine (FT4) with middle cerebral artery and descending thoracic aortic mean blood velocity (MCAVm and AoVm) respectively.

Table 1. Associations between delta values (δ) of fetal TSH or thyroid hormones and delta values of mean blood velocity (Vm) in the middle cerebral artery (MCA) or thoracic aorta (Ao), Po_2 and haemoglobin (Hb) for both rhesus affected and small for-gestational-age fetuses.

	δ MCAVm		δ AoVm		δ Po_2		δ Hb	
	r	*n*	*r*	*n*	*r*	*n*	*r*	*n*
δ TSH	0·23*	76	−0·10	76	−0·18	76	−0·05	76
δ T4	0·20	61	0·41**	61	0·34**	61	−0·26*	61
δ FT4	0·09	69	0·50***	69	0·41**	69	−0·30*	69
δ T3	0·20	59	−0·01	59	0·06	59	0·04	59
δ FT3	0·15	67	0·36**	67	0·17	67	−0·21	67

*$P<0·05$, **$P<0·01$, ***$P<0·0001$.
Delta values = differences of observed values from the normal mean for gestation in SDs, *n* is the number of fetuses measured.

knowledge of the subgroup (red cell isoimmunized or SGA) did not contribute significantly in explaining the variation in fetal TSH after correction for δ MCAVm (F to remove subgroup = 2·97, $P = 0·09$). Similarly, knowledge of the subgroup did not contribute significantly in explaining the variation in δ T4, δ FT4 and δ FT3 after correction for δ AoVm (F to remove subgroup: for T4 = 0·01, $P = 0·92$; for FT4 = 0·00, $P = 0·99$; and for FT3 = 2·05, $P = 0·16$). Furthermore, it was found that after correction for δ AoVm, neither Po_2 nor δ Hb contributed significantly in explaining the variation in δ T4 and δ FT4 (T4: F to remove $Po_2 = 1·46$, $P = 0·23$ and F to remove Hb = 0·01, $P = 0·92$; FT4: F to remove $Po_2 = 1·01$, $P = 0·32$ and F to remove Hb = 0·01, $P = 0·94$).

Discussion

In red cell isoimmunized pregnancies, the fetal haemoglobin is decreased, the fetal circulation is hyperdynamic, and both fetal TSH and thyroid hormones are increased. Some growth-retarded fetuses are hypoxaemic, there is evidence of redistribution in fetal blood flow in favour of the brain and at the expense of the viscera, and thyroid hormone concentrations are decreased while TSH levels are increased. These data confirm the findings of previous studies (Thorpe-Beeston *et al.* 1991b; Thorpe-Beeston *et al.* 1991c; Nicolaides *et al.* 1989b, 1990; Bilardo *et al.* 1990), and in addition demonstrate significant associations between pituitary-thyroid function and Doppler variables.

In SGA and rhesus affected fetuses, the increase in TSH was significantly associated with an increase in blood velocity in the cerebral circulation. Furthermore, the alterations in thyroid hormone concentration were significantly associated with blood velocity in the descending thoracic aorta. The blood vessels supplying the thyroid gland, superior and inferior thyroid arteries and, if present, the thyroidea ima, are presently not amenable to Doppler studies. The superior thyroid artery is a branch of the external carotid artery, the inferior thyroid artery a branch of the thyrocervical trunk and the thyroidea ima artery is a branch of the brachiocephalic artery or arises directly from the aorta. It would be reasonable to assume that alterations in flow velocity waveforms from the descending thoracic aorta, which are currently considered to be representative of visceral and peripheral blood flow (Bilardo *et al.* 1990), also reflect changes in blood flow to the thyroid gland, which does not receive its blood supply from the internal carotid artery.

The blood concentration of hormones is a consequence of the interplay of many factors affecting synthesis, release and consumption. Therefore, it is not surprising that blood flow, as assessed by Doppler, can explain only 5%–25% of the observed variance in TSH and thyroid hormone concentrations. Nevertheless, this study has demonstrated that changes in fetal pituitary-thyroid function may partly be due to altered blood flow to the brain and thyroid glands.

The relation between the change of fetal thyroid function and the haemodynamic alterations observed in anaemic and growth retarded fetuses may be due to the effect of circulatory changes on the growth and function of the fetal pituitary and thyroid glands. In addition, the

observed decrease in thyroid hormones in SGA fetuses may be due to deficiency in essential nutrients as a consequence of reduced uteroplacental perfusion. In red cell isoimmunization, maternal blood supply to the placenta is normal but, in the presence of a hyperdynamic fetal circulation, both nutrient uptake from the placenta and subsequent supply to the thyroid gland are likely to be increased.

Alternatively, the alterations in the concentrations of thyroid hormones, observed in SGA and rhesus affected fetuses, may cause some of the observed differences in the peripheral circulation in these conditions. Thus, animal studies have demonstrated that thyroid hormones have cardiotonic properties (Markowitz & Yater 1932). Furthermore, in human postnatal life, hyperthyroidism is associated with increased cardiac output, stroke volume, heart rate, mean systolic ejection rate and diminished peripheral resistance (Degroot & Leonard 1970), whereas hypothyroidism is accompanied by a reduction in cardiac output. The high serum TSH concentrations found in both SGA and rhesus affected fetuses may be due to pituitary stimulation by catecholamines (Fukuda 1987), which are increased in both conditions (Greenough *et al.* 1990).

Circulatory re-adjustments and alterations in pituitary-thyroid function may be considered as beneficial adaptations to the hostile intrauterine environment in hypoxic growth retardation and anaemia. In the former, relative hypothyroidism slows metabolism, while centralization of flow ensures continuing brain oxygenation. In anaemia, the hyperdynamic circulation improves tissue perfusion, and the increased thyroid hormone concentration may improve tissue oxygenation by stimulating the production of erythropoietin and 2,3 diphosphoglycerate (Das *et al.* 1975; Synder & Reddy 1970; Soothill *et al.* 1988).

References

Bilardo C. M., Campbell S. & Nicolaides K. H. (1988) Mean blood velocities and flow impedance in the fetal descending thoracic aorta and common carotid artery in normal pregnancy. *Early Human Dev* **18,** 213-221.

Bilardo C. M., Nicolaides K. H. & Campbell S. (1990) Doppler measurements of fetal and uteroplacental circulations: Relationship with umbilical venous blood gases measured at cordocentesis. *Am J Obstet Gynecol* **162,** 115-120.

Das K. S., Mukherjee M. & Sarkar T. K. *et al.* (1975) Erythropoiesis and erythropoetin in hypo- and hyperthyroidism. *J Clin Endocrinol Metab* **40,** 211-220.

Degroot W. J. & Leonard J. J. (1970) Hyperthyroidism as a high cardiac output state. *Am Heart J* **79,** 265-275.

Fukuda S. (1987) Correlation between function of the pituitary-thyroid axis and metabolism of catecholamines by the fetus at delivery. *Clin Endocrinol* **27,** 331-338.

Greenough A., Nicolaides K. H. & Lagercrantz H. (1990) Human fetal sympathoadrenal responsiveness. *Early Human Development* **23,** 9-13.

Markowitz C. & Yater W. M. (1932) Response of explanted cardiac muscle to thyroxine. *Am J Physiol* **100,** 162-167.

Nicolaides K. H., Bilardo C. M. & Campbell S. (1990) Prediction of fetal anaemia by measurement of the mean blood velocity in the fetal aorta. *Am J Obstet Gynecol* **162,** 209-214.

Nicolaides K. H., Economides D. L. & Soothill P. W. (1989a) Blood gases, pH, and lactate in appropriate- and small-for-gestational-age fetuses. *Am J Obstet Gynecol* **161,** 996-1001.

Nicolaides K. H., Soothill P. W., Rodeck C. H. & Clewell W. (1986a) Rh Diseases: Intravascular fetal blood transfusion by cordocentesis. *Fetal Therapy* **1,** 185-192.

Nicolaides K. H., Soothill P. W., Rodeck C. H. & Campbell S. (1986b) Ultrasound-guided sampling of the umbilical cord and placental blood to assess fetal well-being. *Lancet* **i,** 1065-1097.

Nicolaides K. H. (1989b) Studies on fetal physiology and pathophysiology in rhesus disease. *Semin Perinatol* **13,** 328-337.

Soothill P. W., Lestas A. N., Nicolaides K. H., Rodeck C. H. & Bellingham A. J. (1988) 2,3-Diphosphoglycerate in normal, anaemic and transfused human fetuses. *Clin Science* **74,** 527-530.

Synder L. M. & Reddy W. (1970) Thyroid hormone control of erythrocyte 2,3 diphosphoglyceric acid concentrations. *Science* **169,** 879-880.

Thorpe-Beeston J. G., Nicolaides K. H., Felton C. V., Butler J. & McGregor A. M. (1991a) Maturation of the secretion of thyroid hormone and thyroid stimulating hormone in the fetus. *New Engl J Med* **24,** 532-536.

Thorpe-Beeston J. G., Nicolaides K. H., Snijders R. J. M., Felton C. V. & McGregor A. M. (1991b) Thyroid function in small for gestational age fetuses. *Obstet Gynecol* **77,** 701-706.

Thorpe-Beeston J. G., Nicolaides K. H., Snijders R. J. M. & Felton C. V. (1991c) Thyroid function in anaemic fetuses. *Fetal Therapy* (in press).

Vyas S., Nicolaides K. H. & Cambell S. (1990) Doppler examination of the middle cerebral artery in anemic fetuses. *Am J Obstet Gynecol* **162,** 1066-1068.

Yudkin P. L., Aboualfa M., Eyre J. A., Redman C. W. G. & Wilkinson A. R. (1987) New birthweight and head circumference centiles for gestational ages 24-42 weeks. *Early Human Dev* **15,** 45-52.

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