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Fetal Thyroid Function

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Key Words
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Abstract
Cordocentesis has permitted the study of fetal thyroid function. In normal pregnancy, fetal blood thyroid-stimulating hormone (TSH), thyroid hormones and thyroid-binding globulin increase with advancing gestation demonstrating functional maturation of the pituitary, thyroid and liver, respectively. The administration of thyroid-releasing hormone to the mother produces a rapid increase in fetal TSH from at least 25 weeks gestation. In hypoxemic growth-retarded fetuses, the concentrations of TSH are higher, and the concentrations of total and free thyroxine are lower than in appropriately grown fetuses. In anemic fetuses from red cell-isoimmunized pregnancies, serum TSH and thyroid hormone concentrations are increased. In some chromosomally abnormal fetuses, particularly those with trisomy 21, TSH is increased.

Thyroid hormones have played a role in vertebrate life since the days when primitive crossopterygian fish ruled the seas, and they have been found in all forms of vetebrates from the lamprey larva to modern man [1]. In some species the role of these hormones has been extensively studied, for example in amphibians, where they have been shown to be essential in metamorphosis. Although knowledge of their role in mammals is more scanty, studies in rats, sheep and monkeys have shown that thyroid hormones are essential for

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optimal growth and development of the central nervous system, lung, gut and liver, and regulation of carbohydrate, protein and lipid metabolism [2, 3]. In the human, failure of the orderly maturation of the hypothalamic-pituitary-thyroid axis results in well-recognized clinical sequelae, manifested at their extreme by cretinism. In addition to intrinsic defects of the pituitary-thyroid axis, abnormalities of thyroid function may also become apparent in nonthyroid illness, such as malnutrition, diabetes mellitus, liver disease or chronic renal failure [4].

Thyroid Function in Normal Human Fetuses

Knowledge of pituitary and thyroid development in human fetuses is based largely on histological studies of abortuses or blood samples obtained in early pregnancy at hysterotomy for elective abortion and in later pregnancy at delivery [5–8]. However, the results derived from samples obtained at the time of hysterotomy or cesarean section may have been influenced by maternal fasting or transient hypotension which could alter placental perfusion and therefore affect the supply of oxygen and nutrients to the fetus [9]. Furthermore, samples obtained after premature delivery may not be representative of normal prelabor values, since thyroid-stimulating hormone (TSH) levels undergo marked and rapid changes in the immediate postnatal period. Indeed, the condition causing premature delivery itself could influence fetal serum TSH and thyroid hormone levels as it is unlikely that fetuses delivered before 37 weeks gestation can truly be described as normal. Despite their limitations, such studies indicate that the thyroid gland begins to produce thyroxine (T_4) at 10–12 weeks gestation [10, 11]. However, there is conflicting evidence as to the age of gestation at which functional maturation of the fetal pituitary-thyroid axis is achieved. Some authors suggest that TSH secretion is responsive to changes in serum-free T_4 concentrations as early as 11 weeks [5]; others suggest that such maturation occurs largely during the last half of pregnancy [6, 7, 12].

Ballabio et al. [13] employed cordocentesis to study fetal thyroid function at 18–31 weeks gestation, and demonstrated that fetal serum TSH, and total and free T_4 concentrations increased with gestation. Fetal serum TSH levels were always higher and total T_4 always lower than adult values, whereas free T_4 reached adult levels by 28 weeks of gestation. They explained these findings by suggesting that the threshold for negative feedback from thyroid hormones on the pituitary is set at a higher level in fetal than in postnatal life. However, the extent to which the findings of this study represent physiological changes in normal fetuses is uncertain because the study group was small (23 fetuses) and the majority (15 cases) were severely anemic due to red cell isoimmunization.

In a more extensive study, involving 62 fetuses undergoing cordocentesis for prenatal diagnosis and subsequently found to be normal, Thorpe-Beeston et al. [14] demonstrated significant increases in concentration with gestation for fetal serum TSH, thyroxine-binding globulin (TBG) and both free and total thyroxine and triiodothyronine (T_3) (fig. 1–4).

There were no significant associations between fetal and maternal serum thyroid hormones and TSH concentrations [7, 14], suggestsing that in the human fetus the pituitary-thyroid axis develops independently from that of the mother. This is different from other species such as the rat, where maternal thyroid hormones play an important role in fetal life [15].

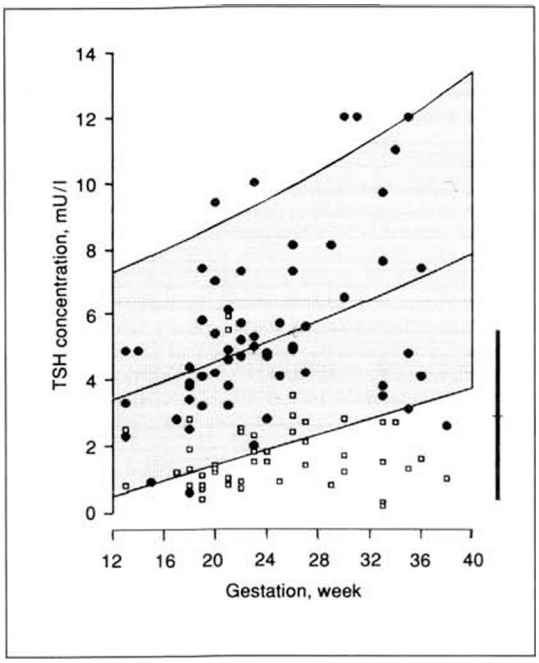
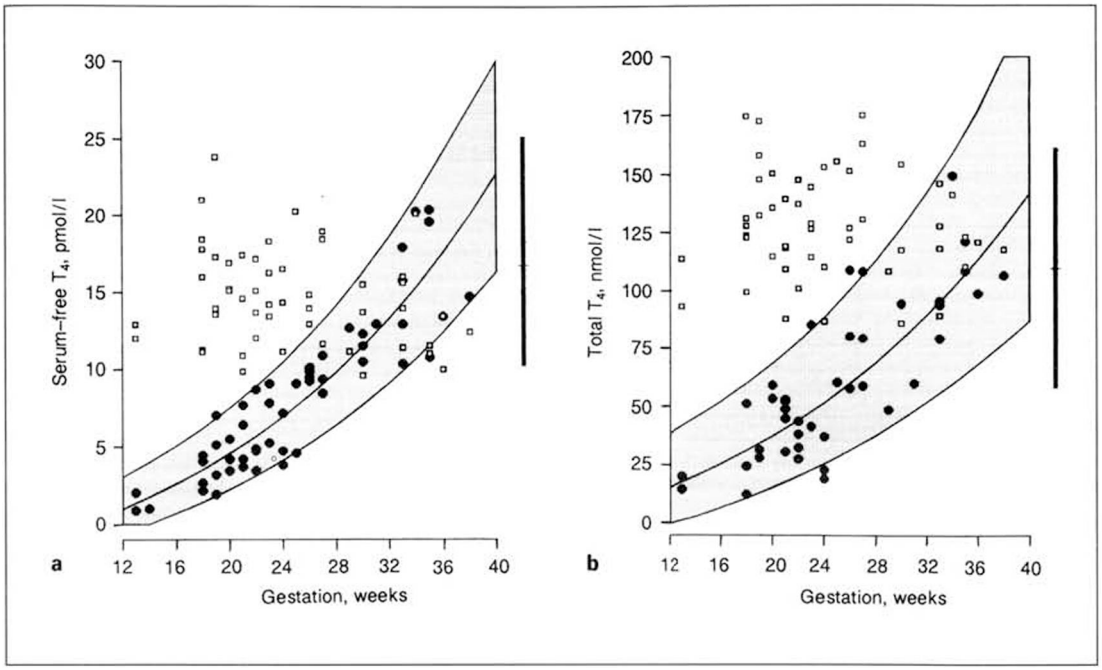


Fig. 1. Individual fetal (●) and maternal (□) values of serum TSH concentration in normal fetuses plotted on the fetal reference range (mean, 5th and 95th centiles). The vertical line on the right is the normal nonpregnant adult range [14, with permission].

Although fetal total and free T_4 serum concentrations reached adult levels by 36 weeks gestation, the fetal total and free T_3 concentrations were always less than half the respective mean adult concentrations (fig. 2, 3) [14]. The major source of free T_3 is peripheral conversion of T_4, and therefore these findings suggest that in intrauterine life the mechanisms necessary for this conversion are either immature or lack the necessary stimulus for their activation. In vitro studies in sheep have demonstated that there is a dramatic increase in the capacity for hepatic conversion of T_4 to T_3 during labor and into the neonatal period [16]. Similarly, Fisher et al. [7] showed that in the human there is a tenfold increase in the ratio of serum T_3 to T_4 from 30 weeks gestation to 1 month postnatally. An alternative explanation for the low fetal T_3 concentrations could be rapid deiodination by the placenta.

The increase in fetal thyroid hormone concentrations with gestation reflects the increasing maturation of the fetal thyroid gland. The lack of correlation between TSH and most thyroid hormones, independent of gestation, suggests that the thyroid gland matures independently of the influence of TSH. Alternatively, the increasing levels of thyroid hormones may be a consequence of improved placental transfer of nutrients with gestation. Although a recent study by Vulsma et al. [17] of infants with severe congenital hypothyroidism suggested that a substantial amount of T_4 is transferred from mother to fetus, the cord blood levels of T_4 at term were only 30–70 nmol/l. Therefore, it is likely that the bulk of fetal T_4 is derived from fetal thyroid secretion. Furthermore, this study was performed in hypothyroid fetuses and infants and therefore its relevance to normal fetuses may be questioned.

Fetal serum TSH increased significantly with gestation and the concentration is always higher than in the mother (fig. 1) [14]. In postnatal life the major determinant of negative feedback is intrapituitary T_3, originating from the local monodeiodination of T_4 [18]. In the present study, there was a gestational age-independent positive association between free T_4 and TSH, and even in the third trimester when adult concentrations of total and free T_4 were reached, TSH concentration continued to rise. These findings suggest that the fetal pituitary is relatively insensitive to negative feedback from thyroid hormones or is sensitive to increasing stimulation by thyrotropin-releasing hormone (TRH). Alternatively, in the fetus circulating free T_3 has a more important role in feedback than in the



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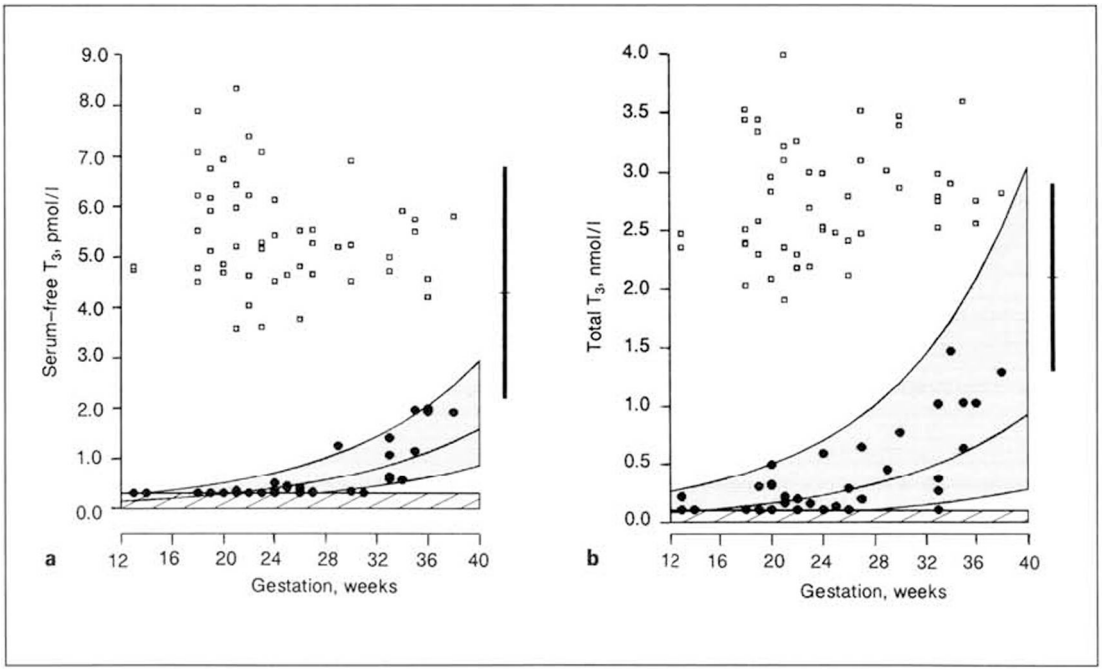

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Fig. 2, 3. Individual fetal (●) and maternal (□) values of serum-free (**a**) and total (**b**) and T_4 (**2**) and T_3 (**3**) concentrations in normal fetuses plotted on the fetal reference ranges (mean, 5th and 95th centiles). The vertical lines on the right are the normal nonpregnant adult ranges [14, with permission].

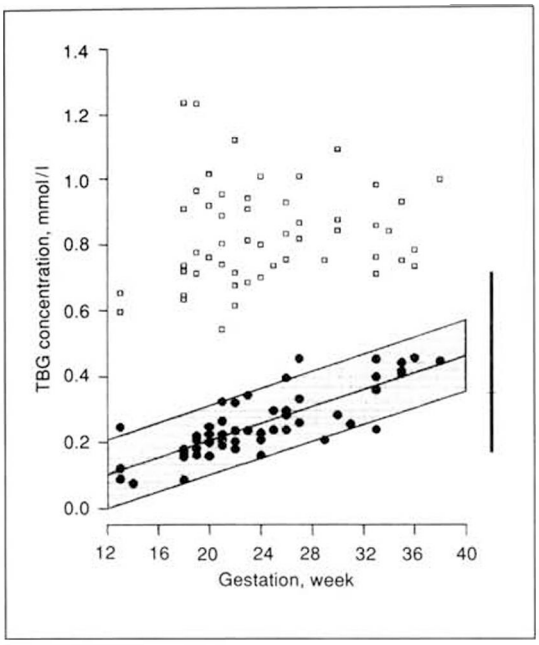

Fig. 4. Individual fetal (●) and maternal (□) values of serum TBG concentration in normal fetuses plotted on the fetal reference range (mean, 5th and 95th centiles). The vertical line on the right is the normal nonpregnant adult range [14, with permission].

adult. Since in the fetus the concentration of free T_3 is much lower than in postnatal life, the threshold for negative feedback is never reached in utero and therefore the high TRH concentration may be a consequence of fetal pituitary hyperactivity in the presence of a hypothyroid intrauterine environment.

Fetal serum TBG concentration increased with gestation and reached adult levels during the third trimester (fig. 4) [14]. This probably reflects the functional maturation of the fetal liver and its increasing capacity to manufacture proteins; fetal albumin concentration also increases with gestation [19]. The lack of significant association between TBG and thyroid hormones, independent of gestation, provides further evidence for the relative functional immaturity of the fetal pituitary-thyroid axis.

Fetal Response to Maternal TRH

In fetal life, thyroid hormones play a major role in pulmonary development, and animal studies have demonstrated improvement in fetal pulmonary maturation after the intra-amniotic or direct fetal injection of T_3 or T_4 [10–22].

Human studies have demonstrated very limited transplacental transfer of thyroid hormones, and the necessary dose to achieve an effect on the fetus has toxic effects on the mother [23, 24]. Amniocentesis, as a mechanism for introducing thyroid hormones to the fetal environment has provided conflicting results. Although in one study the intra-amniotic instillation of T_4 produced a significant improvement in the degree of lung maturation, Schreyer et al. [25] investigating the influence of intra-amniotic T_3, reported that T_3 and TRH values in the umbilical cord blood at delivery were not significantly different from those of controls, and it was concluded that there was no positive effect after T_3 administration.

An alternative method to increase the concentration of thyroid hormones in fetal blood is by maternal administration of TRH, which unlike thyroid hormones crosses the placenta readily. Roti et al. [26] administered TRH at timed intervals before delivery and measured TSH and thyroid hormones in cord blood at delivery. TSH was significantly elevated within 20 min, while T_3 rose significantly by 60 min and T_4 by 120 min. The findings demonstrated that (1) TRH crosses the placenta; (2) the fetal pituitary at term is responsive to TRH, and (3) endogenous TRH stimulates the fetal thyroid. Supportive evidence for this work was presented by Moya et al. [27].

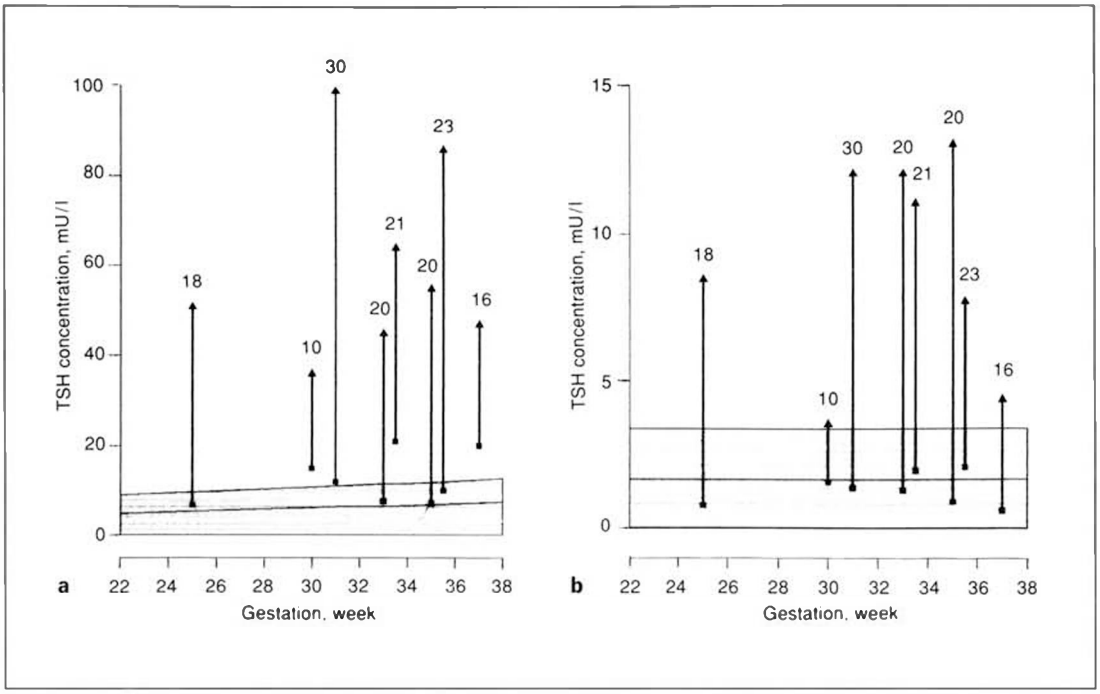

Fig. 5. Increase in fetal (**a**) and maternal (**b**) blood concentration of TSH (mU/l) within 10–30 min from the administration of TRH to the mother (actual time interval given above TSH response in each case), plotted on the appropriate reference ranges (mean, 5th and 95th centiles) for gestation (top) [28, with permission].

Recently, Thorpe-Beeston et al. [28] administered TRH to mothers with red blood cell isoimmunization who were undergoing cordocentesis for fetal blood transfusion at 25–37 weeks gestation. Serum TSH was measured in maternal and umbilical venous blood samples obtained immediately before and after fetal blood transfusion. This study demonstrated that (1) maternal administration of TRH is associated with a rapid increase in fetal TSH (fig. 5); (2) the magnitude of the fetal response does not change within the gestational range that was studied (25–37 weeks), and is similar to that reported in fetuses undergoing TRH stimulation at term [26, 27], and (3) the fetal response to TRH is much greater than the maternal and this increased sensitivity may be a consequence of reduced negative feedback on the pituitary because of relative intrauterine hypothyroidism.

If maternal TRH is to be used to enhance fetal pulmonary development, further studies would be necessary to define the optimal dosage of TRH and the time course of the response. There is some evidence that multiple doses of TRH administered to preterm rabbits may induce pulmonary maturation, but with a higher perinatal mortality rate than if TRH is used in single doses [29]. In a human study, Morales et al. [30] demonstrated that the combined use of corticoste-

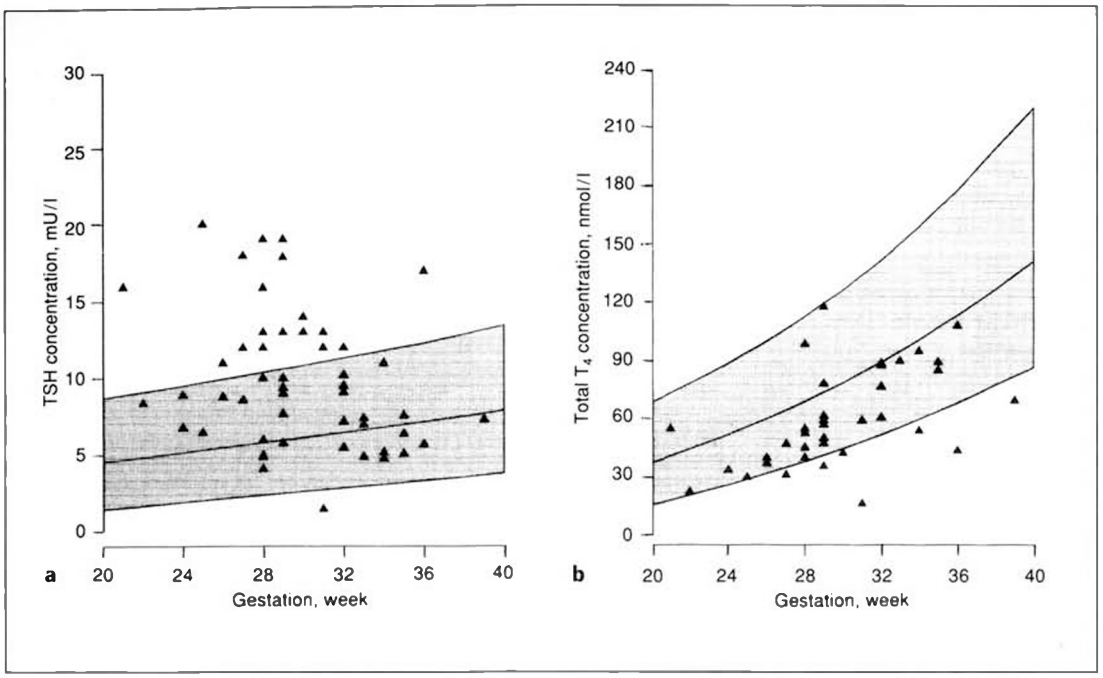

Fig. 6. Individual values of fetal serum TSH (**a**) and total T_4 (**b**) concentrations in 49 growth-retarded fetuses plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation [33, with permission].

roids and TRH enhanced fetal lung maturation to a greater degree than corticosteroids alone.

Thyroid Function in Gowth-Retarded Fetuses

In postnatal life, malnutrition is associated with disturbance in thyroid function [31, 32]. In a study of hypoxemic gowth-retarded fetuses due to uteroplacental insufficiency, thyroid function was studied in umbilical venous blood samples obtained by cordocentesis at 22–38 weeks gestation [33]. TRH was higher and thyroid hormones were lower than in normal fetuses (fig. 6). Furthermore, the magnitude of the observed derangement in the pituitary-thyroid axis was related to the degree of fetal hypoxemia and acidemia.

Reduced synthesis of thyroid hormones may be due to either impaired placental perfusion and consequent reduction in the supply of essential nutrients and/or hypoxic suppression of thyroid function. Alternatively, since in normal fetuses there is a gestation-related maturation of the thyroid gland [14], the low thyroid hormone concentration in growth-retarded fetuses may be due to developmental delay.

Although hypothyroidism, with a consequent decrease in metabolic rate and oxygen consumption, may represent a beneficial adaptation to the fetal starvation observed in

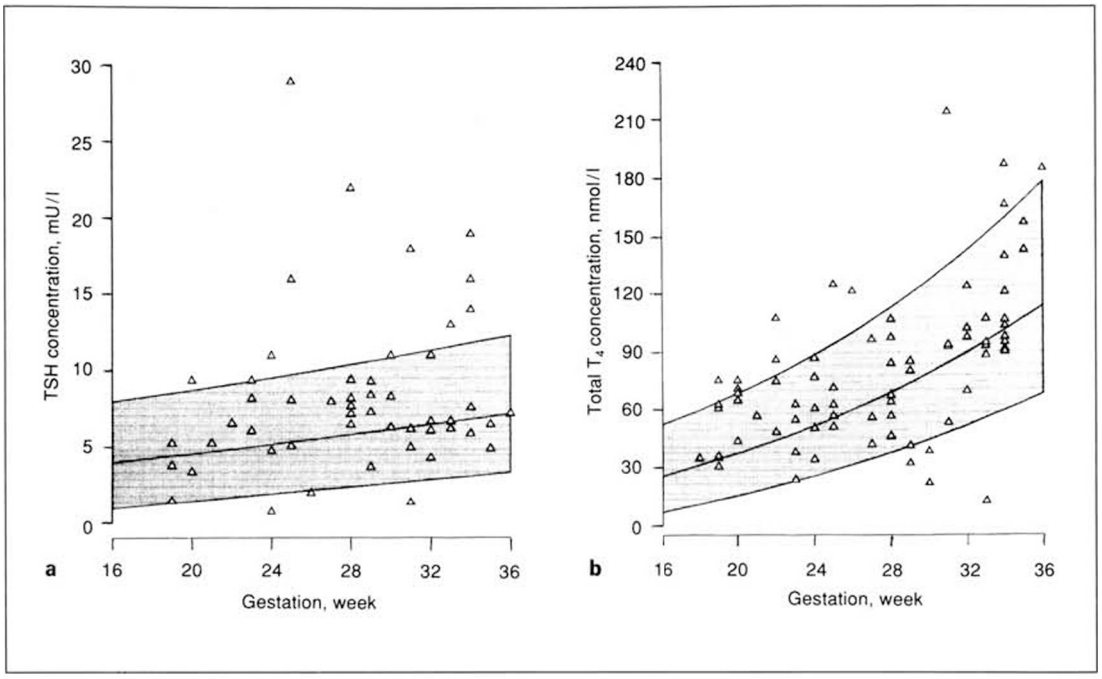

Fig. 7. Individual values of fetal serum TSH (**a**) and total T_4 (**b**) concentrations in 75 red cell-isoimmunized pregnancies plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation [39, with permission].

uteroplacental insufficiency, the concomitant increase in TRH concentration suggests that the low concentration of thyroid hormones does not constitute a purposeful adaptive mechanism. Indeed, hypothyroidism may adversely affect the fetus because thyroid hormones have a critical role in the growth and functional development of the brain [15, 34]. Although in congenital hypothyroidism prompt therapy in the postnatal period usually prevents adverse neurological sequelae [35], early-onset intrauterine hypothyroidism could result in irreversible brain damage and may be one of the underlying causes of mental handicap in such infants.

The increased serum TRH in growth-retarded fetuses may be due to pituitary stimulation by (1) low thyroid hormones; (2) increased catecholamines, found in hypoxemic growth retardation [36, 37], or (3) increased brain perfusion [38].

Thyroid Function in Anemic Fetuses

Thyroid function was studied in 75 fetal blood samples obtained by cordocentesis from red cell-isoimmunized pregnancies at 18–37 weeks gestation [39]. TRH and both free and total T_3 and T_4 were significantly higher than in normal controls (fig. 7). Furthermore, there was a significant association between the increase in TSH and the degree of fetal anemia.

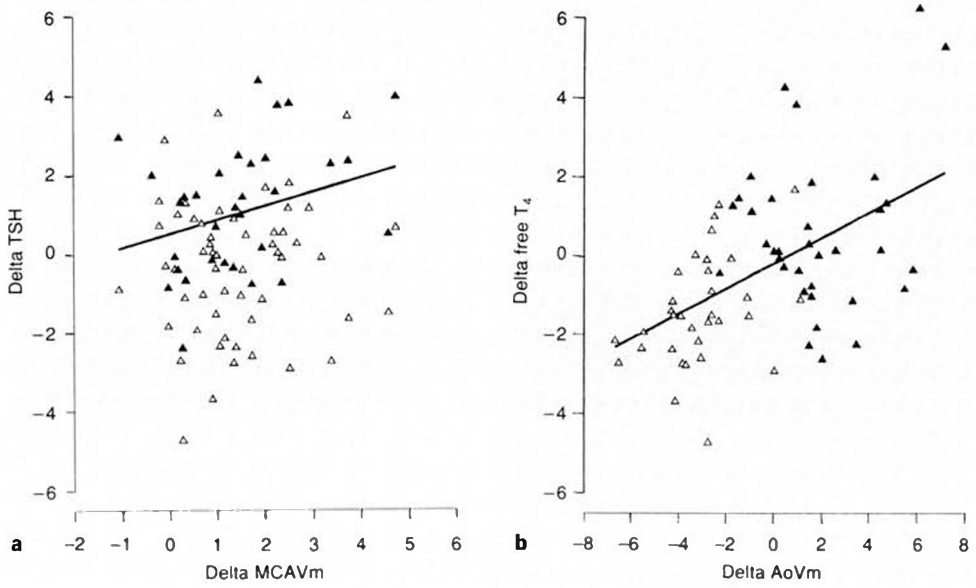

Fig. 8. Relation of delta values in small for gestational age (△) and rhesus-affected (▲) fetuses (in SD from the appropriate mean of gestation) for fetal TSH (**a**) and free T_4 (**b**) with middle cerebral artery and descending thoracic aortic mean blood velocity (MCAVm and AoVm), respectively [46, with permission].

The observed increase in thyroid hormone concentration, would confer several possible benefits on the anemic fetus. Thus, thyroid homones 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 [40, 41]. Furthermore, thyroid hormones stimulate the production of erythropoietin and 2,3-diphosphoglycerate [42, 43], both of which are known to be increased in anemic fetuses [44, 45], with consequent incrase in red cell production and improvement in oxygen release to the tissues.

The increase in both TSH and thyroid hormones provide further evidence for the autonomy of the pituitary and thyroid glands in intrauterine life [14]. 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 [36, 37]. An alternative explanation for the apparent pituitary hyperactivity is increased brain perfusion. The thyroid hyperactivity may be due to the increased level of TSH.

A unifying hypothesis that could explain the findings in both hypoxemic growth-re-

tarded and red cell isoimmunization fetuses is that the activity of the fetal pituitary and thyroid glands is a consequence of the hemodynamic alterations in these conditions (fig. 8) [46]. 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.

Thyroid Function in Chromosomally Abnormal Fetuses

Although the reported prevalence of thyroid disorders in Down's syndrome varies from 0.7 to 37%, it is accepted to be much higher than in the general population [47, 48]. There is evidence that early diagnosis and effective treatment may not only improve the physical well-being of such infants, but may also have a significant impact on intellectual function [49].

TSH, free and total T_3 and T_4 were measured in blood samples obtained by cordocentesis from 15 chromosomally abnormal fetuses [50]. The indication for cordocentesis was fetal karyotyping after detection of fetal malformations by ultsonography. In all 5 fetuses with trisomy 21, in 2 of the 5 with trisomy 18, and in 1 of the 2 with triploidy, TSH was above the 95th centile of the reference range (fig. 9). However, thyroid hormone concentrations in all 15 chromosomally abnormal fetuses were within the reference ranges, and the mean values were not significantly different from the normal means for gestation.

The high TSH in some chromosomally abnormal fetuses, particularly those with trisomy 21, may be an early manifestation of relative hpyothyroidism and may be one of the underlying causes of mental handicap in such infants. The extent to which intrauterine hormone supplementation would reduce impaired neurological development remains to be determined.

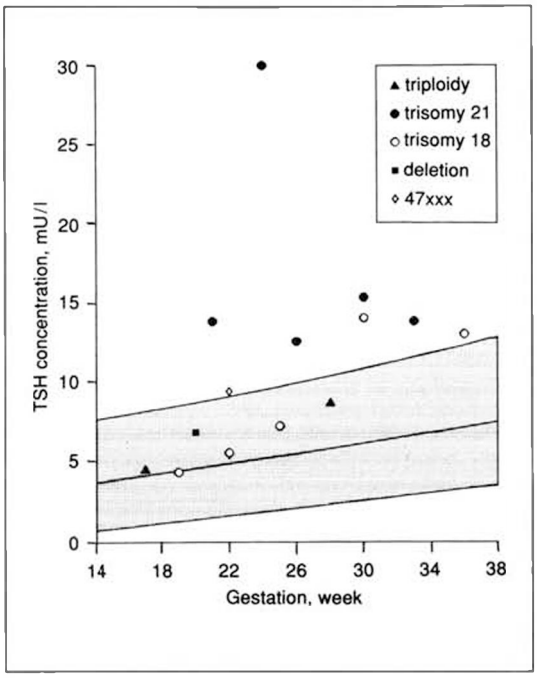

Fig. 9. Serum TSH concentration in chromosomally abnormal fetuses plotted on the reference range (mean, 5th and 95th centiles) for gestation [50, with permission].

Conclusions

Cordocentesis has permitted the study of fetal thyroid function in utero. During the second trimester of pregnancy, it is likely that the increase in fetal blood TSH, thyroid hormones and TBG represent independent and autonomous maturation of the pituitary, thyroid and liver, respectively. With advancing gestation there is a rise in thyroid hormones

reflecting functional maturation of the thyroid gland. Despite this, the concentrations of fetal total and free T_3 are always lower than in postnatal life, and in intrauterine life there is uninhibited production of TSH. The findings of increasing fetal serum TSH in the face of increasing fetal thyroid hormone concentrations suggest that the fetal pituitary gland is not susceptible to negative feedback in utero.

The maternal administration of TRH from at least 25 weeks gestation stimulates the fetal pituitary gland to produce TSH. The response is rapid, unrelated to gestational age, and much greater than that of the mother. The extent to which the maternal administration of TRH may improve fetal lung maturation remains to be determined.

In hypoxemic growth-related fetuses the concentrations of TSH are higher, and the concentrations of total and free T_4 are lower than in appropriately grown fetuses. Although the low concentrations of thyroid hormones may have some beneficial effects, by reducing oxygen requirements, they may adversely affect brain development and could be one of the underlying causes of mental handicap in such infants.

In red cell-isoimmunized pregnancies TSH and thyroid hormone concentrations are increased. These changes would confer several possible benefits on the anemic fetus, having 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, leading to improved tissue oxygenation.

A unifying hypothesis that could explain some of the observed changes in fetal pituitary and thyroid function in both hypoxemic growth retardation 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.

In some chromosomally abnormal fetuses, particularly those with trisomy 21, TSH is increased. This may be an early manifestation of relative hyopthyroidism that could be one of the underlying causes of mental handicap in such fetuses.

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