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Fetal Thyroid Function

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ABSTRACT

Cordocentesis has permitted the study of fetal thyroid function in utero. In normal fetuses, fetal TSH, TBG, and thyroid hormone concentrations increase progressively throughout intrauterine life. Fetal TSH concentrations are always high compared to nonpregnant adult values. TBG concentrations reach adult levels at term. TT_4 and FT_4 concentrations reach adult levels at approximately 36 weeks gestation, but TT_3 and FT_3 are always below adult concentrations. There are no significant associations between fetal and maternal concentrations of TSH, TBG, or thyroid hormones. 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. These findings suggest that in intrauterine life there is independent and autonomous maturation of the pituitary, thyroid, and liver. The fetal pituitary is able to respond to the maternal administration of TRH and appears to be more sensitive than in the adult. In small-for-gestational-age fetuses, the concentrations of TSH are higher and the concentrations of TT_4 and FT_4 are lower than in appropriately grown fetuses. The degrees of elevation of TSH and fall in thyroid hormones are significantly related to the degree of fetal hypoxemia and acidemia, respectively. Although the low concentrations of thyroid hormones may have some beneficial effects by reducing oxygen requirements, they may adversely affect brain development.

INTRODUCTION

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 vertebrates from the lamprey larva to modern humans (1).

The actions of thyroid hormones are determined by several factors, including the animal species, type of tissue, hormone level, duration of time the tissues are exposed, and the influence of other hormones. In some species, the role of these hormones has been studied extensively, for example, in amphibians, where they have been shown to be essential in metamorphosis. In mammals, knowledge is more scanty. Nevertheless, studies in rats, sheep, and monkeys have shown that thyroid hormones are essential for optimal growth and development of the central nervous systems (2,3), gut (4,5), liver (6,7), and lung (8,9), regulation of amino acid and electrolyte transport in the cell, modulating carbohydrate, protein, and lipid metabolism, and augmenting oxidative phosphorylation rates (10–12).

In adult humans, thyroid hormones produce effects that differ qualitatively from tissue to tissue, as exemplified by the enhancement of lipoprotein activity in adipose tissue, the modulation of gonadotropin secretion by the pituitary, and maintenance of proliferative cell growth and maturation of hair. In liver, kidney, and muscle, thyroid hormones stimulate both sodium pump and glycolytic pathways (13,14). In the brain, thyroid hormones alter neurotransmitters and their receptors (15,16).

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 also may become apparent in nonthyroid illness, for example, malnutrition, diabetes, chronic renal or liver disease, or in response to surgery (17).

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INVESTIGATION OF FETAL THYROID FUNCTION

Animal studies

The results of work in animals has suggested three phases of fetal thyroid ontogenesis: embryogenesis, hypothalamic maturation, and development of the hypothalamic-pituitary-thyroid system control. The two best studied animals are the rat and sheep (10). In the latter at 46–48 days of gestation (term is 150 days), the gland is well formed and by 70 days resembles the adult gland histologically and has been shown, by autoradiographs, to contain T_4 and T_3. In the sheep, pituitary TSH has been identified from 50 days and increases progressively with gestation. There is a marked and progressive increase in serum T_4 concentrations from midgestation (18,19).

Data regarding maturation of the TRH response and of negative feedback control in the sheep are sparse. Erenberg et al. have shown that the sheep fetus during the last trimester reponds to thyroidectomy with a rapid decrease in serum T_4 and a marked increase in serum TSH concentrations (20), whereas hypophysectomy during the same period results in rapid decreases in both serum TSH and T_4 levels (21). Exogenous T_4 administered to near-term fetal sheep suppresses TSH secretion, whereas TRH stimulates both TSH and prolactin secretion (22). These data provide evidence that TRH responsiveness and negative feedback do exist during the last trimester of pregnancy in fetal sheep, but data regarding timing of maturation of these responses are lacking.

In the rat, embryogenesis extends throughout the period of intrauterine development, which is 23 days. The thyroid gland is well formed and, by 17 days, is able to concentrate radioiodine. By 20 days, the gland can synthesize T_3 and T_4 (23). There is parallel development of the pituitary gland, and between day 19 and the sixth postnatal day, there is a progressive increase in the number of granular cells and the number of granules per cell in the adenohypophysis. TSH is present in the rat pituitary from 17 days of gestation. In the newborn rat pup, TSH, T_3, and T_4 concentrations are initially low, increasing to reach peak levels by 10–12 days of postnatal life. It has been suggested that, in the rat, there is progressive and parallel maturation of both the thyroid and hypothalamic-pituitary axis. The increasing levels of TSH stimulate thyroid hormone production (10). The negative feedback sensitivity to thyroid hormones appears to increase during the first 2 weeks of postnatal life.

Human studies

The initial human studies, relying on fetal tissue or blood samples obtained by hysterotomy, have shown that the thyroid gland acquires the capacity to concentrate radioiodine and synthesize iodothyronines by 10–12 weeks of gestation, and TSH, thyroxine, and TBG have been detected in fetal serum as early as 11 weeks of gestation (24–26). This provided data concerning thyroid function up to 24 weeks gestation. Study of human fetal thyroid function after this time relied on blood samples obtained from the umbilical cord after premature delivery (10,27,28).

Greenberg et al. (25) obtained blood samples from 21 normal human fetuses at 11–24 weeks gestation after therapeutic abortion by hysterotomy. The TSH, T_4, and FT_4 increased linearly within this gestational range and reached term levels by 16–20 weeks. The authors postulated that the parallel changes and direct correlation of FT_4 and TSH concentrations indicated that TSH secretion was responsive to FT_4 from as early as 11 weeks gestation and that it was unlikely that the parallel changes represented independent maturation of the glands. In this study, fetal TSH levels after 16 weeks gestation were above adult levels, but the authors did not comment on this finding. TBG levels increased until term. There was no significant correlation between maternal TSH levels and any of the parameters of fetal thyroid function, and it was suggested that this reflected the inability of maternal TSH to cross the placenta.

These results of Greenberg et al. (25) conflict with those of two other studies of fetal blood samples obtained at hysterotomy or delivery at 24–43 weeks gestation. Thus, Fisher et al. (27) and Klein et al. (28) reported that TSH did not change within this gestational range, T_3 and FT_3 increased sharply with gestation after 28 weeks, and T_4 and FT_4 increased linearly from 26 to 34 weeks and then remained constant. They suggested that during the last half of pregnancy, there is increasing maturation of the fetal thyroid gland responsiveness to TSH and a progressive decrease in pituitary thyrotroph sensitivity to T_3.

Ballabio et al. examined thyroid function in samples obtained by cordocentesis in 23 subjects at 18–31 weeks gestation (29). This study demonstrated that fetal TSH, T_4, and FT_4 increased linearly with gestation and confirmed earlier work that fetal TSH levels were higher than adult levels. T_4 was always lower than adult values, whereas FT_4 reached adult levels by 28 weeks gestation. It was suggested that the threshold for negative feedback from thyroid hormones on the pituitary is set at a higher level than in postnatal life.

Limitations of previous studies

The present knowledge of human fetal thyroid function has been derived primarily from animal experiments and studies in humans at hysterotomy, elective cesarean section, or vaginal delivery. Although these studies have provided an insight into thyroid function in human fetal life, they suffer from various drawbacks. The results of animal studies and the bearing they may have on human fetal thyroid function require careful interpretation because there is great interspecies variation in not only the ability of thyroid hormones to cross the placenta but also in regard to the specific biologic and cellular effects of the hormones (30).

Data derived from samples obtained after hysterotomy or cesarean section may have been influenced by maternal fasting and episodes of transient hypotension, which could affect placental perfusion and the supply of oxygen and nutrients to the fetus (31,32). Samples obtained after premature delivery may not necessarily be representative of normal prelabor values. The stress of labor influences greatly the levels of most metabolites and hormones, and some hormonal changes precede labor. Furthermore, TSH levels undergo marked and rapid changes in the immediate postnatal period (27). Study of umbilical cord blood samples obtained before term may not be representative of values in normal fetuses, as the condition causing premature delivery itself could influence fetal thyroid levels. Furthermore,

it is unlikely that populations of fetuses being delivered before 37 weeks gestation can truly be described as normal.

CORDOCENTESIS

Access to the fetal circulation was achieved originally by hysterotomy (33). Subsequently, with the development of fiberoptics, fetoscopy was used to visualize and sample vessels on the chorionic plate and the umbilical cord (34,35). Cordocentesis (ultrasound-guided puncture of the umbilical cord) is the current method of choice for fetal blood sampling (36,37).

Cordocentesis has allowed access to the fetal circulation and permitted detailed study of fetal biochemistry and metabolism (37). Reference ranges for gestational age have been established for fetal blood gases, glucose, lactate, amino acid, and triglycerides (38–40). Subsequently, studies in fetuses suffering from intrauterine growth retardation have demonstrated that some of these fetuses are hypoxemic, hypercapneic, hypoglycemic, and starved of essential amino acids (38–40). Many of these abnormalities have been shown to correlate with the degree of fetal hypoxemia. Using another model of tissue hypoxia, anemic fetuses affected by rhesus disease, changes in fetal oxygenation have been demonstrated and have been shown to be related to the degree of fetal anemia (41). Cordocentesis now permits the study of fetal thyroid function in both normal fetuses and those submitted to stress. Furthermore, it has become possible to examine the response of the fetal pituitary-thyroid axis to external manipulation.

The safety of cordocentesis is now well documented, with large series reporting only 7 fetal losses in 606 consecutive cases and no losses in 200 cases where cordocentesis was performed for prenatal diagnosis (42,43). In the Harris Birthright Centre for fetal Medicine, King's College Hospital, considerable expertise has accumulated from the study of more than 2500 patients during the last 5 years. In a series of 710 cases sampled for prenatal diagnosis of genetic disease (e.g., thalassaemia) or for karyotyping in cases of minor fetal malformations (e.g., hydronephrosis), there were 7 fetal deaths at 1–20 weeks after the procedure, giving a procedure-related fetal loss rate of approximately 1%. The procedure-related risk would be even lower if cordocentesis were undertaken at a gestational age at which the fetus is mature enough to be delivered if fetal bradycardia or premature labor occurs.

Theoretical complications of cordocentesis include chorioamnionitis, the risks of which are minimized by diligent adherence to aseptic principles. Placental separation is unlikely, since chorionic villus sampling, where a deliberate attempt is made to obtain placental biopsies through a much wider bore needle than the blood sampling needle, is not associated with an increase in the incidence of abruptio placentae. Experience with fetoscopy has shown that withdrawal of the needle after sampling results in minimal bleeding from the cord, which stops within seconds even in fetuses with coagulation defects, such as hemophilia. In cordocentesis, an umbilical vessel is approached transplacentally in more than 60% of cases without the need for cord puncture, and, therefore, there is no intraamniotic bleeding. To avoid the risk of Rh isoimmunization, anti-D (250 μg) is administered to Rh-negative mothers at the end of the procedure, since fetomaternal hemorrhage can occur, especially in the case of transplacental cordocentesis (44).

STIMULATION OF FETAL THYROID FUNCTION

More than 80% of all neonatal deaths and long-term morbidity occur in infants born before 34 weeks gestation. The leading cause is respiratory distress syndrome (RDS), which is associated both with immediate problems in the neonatal period and with chronic lung disease. The antenatal administration of corticosteroids to mothers at risk of premature delivery has been the mainstay of efforts to increase fetal lung maturation. Although this form of therapy is widely adopted, there is increasing scepticism as to its efficacy. Thus, the possible beneficial effect of these agents occurs after a minimum of 24 h, is confined to singleton pregnancies at 28–33 weeks gestation, and appears to be sex and race dependent (45–47).

The limitations of corticosteroids have stimulated the search for alternative methods aimed at preventing RDS. There is substantial evidence that thyroid hormones play a major role in pulmonary development, and animal studies have demonstrated improvement in fetal pulmonary maturation after maternal administration of TRH or intraamniotic or direct fetal injection of T_3 or T_4 (48–50).

Furthermore, knowledge that thyroid function in postnatal life is frequently disturbed in debilitating conditions, such as malnutrition and chronic disease, suggests that if similar alterations are found in fetal models of chronic disease, it may be possible to alter the fetal thyroid status beneficially by external manipulation.

A variety of mechanisms exist that may potentially stimulate fetal thyroid function, including administration of thyroid hormones to the mother or direct instillation of thyroid hormone into the amniotic cavity by amniocentesis. Alternatively, TRH, a small molecule that easily crosses the placenta, can be administered intravenously to the mother. Studies assessing the possibility of fetal thyroid stimulation have mainly addressed the issue of achieving increased pulmonary maturation and only rarely directly assessed fetal thyroid function.

Animal studies

The earliest report suggesting that it would be possible to stimulate fetal thyroid function was by Wu et al. (51). They studied the effect of thyroxine on the development of fetal rabbit lungs. Intramuscular T_4 injection to pregnant rabbits 2 days before premature delivery at 26–28 days gestation (full term is 31 days) failed to accelerate lung maturation as compared with controls. In contrast, the injection of T_4 directly into the fetuses and amniotic sacs in one uterine horn at 24–25 days gestation was associated with greater fetal lung maturation, assessed by electron microscopy, than in controls (fetuses in the other horn into which saline was injected). Although fetal T_4 levels were not measured, this report provides indirect evidence of augmented fetal thyroid function.

Devaskar et al. demonstrated that intramuscular administration of T_3 to the pregnant rabbit was associated with significantly increased fetal plasma T_3, and increased levels of T_3 were

associated with enhanced functional fetal lung maturation (52). Similarly, Gross et al. injected T_3 into pregnant rats on days 18 and 19 of gestation and measured fetal T_3 concentrations on day 20 (53). There was a significant increase in serum T_3 levels as compared with controls. The injection also had the effect of stimulating choline incorporation into phosphatidyl choline, possibly enhancing lung maturation.

There is conflicting evidence in animals concerning the ability of maternally administered TRH to stimulate fetal thyroid function. TRH, T_3 and betamethasone when used alone or in combination significantly increased surfactant production and decreased ventilation requirements in treated and prematurely delivered rabbits. T_4 concentrations measured in cord plasma samples were too low for detection, whereas T_3 levels increased only in those fetuses whose mothers had received T_3 (54). Devaskar et al. noted enhanced functional and morphologic lung maturation in rabbits treated with TRH when compared with controls, but there was no significant increase in T_3 or FT_3 concentrations measured in cord blood (55).

Human studies

Maternal administration of T_4 or T_3 increased fetal cord blood thyroid hormone concentrations (56,57). However, the large doses administered were sufficient to cause maternal hyperthyroidism, and the technique has not been repeated (56,57). Amniocentesis as a mechanism for introducing thyroid hormones to the fetal environment has provided conflicting results. Intraamniotic instillation of T_4 (0.25 mg) was performed by amniocentesis in 16 high-risk pregnancies between 29 and 34 weeks gestation (50). There was a significant improvement in the degree of lung maturation, although fetal thyroid hormone concentrations were not measured. It was suggested that the beneficial effect was secondary to T_3 stimulation of lung maturation, following the conversion of T_4 to T_3. However, Schreyer et al. investigated the influence of intraamniotic T_3 administration on fetal plasma levels of T_3 and TSH and on fetal outcome in patients with impending premature delivery and hypertensive disorders in pregnancy (49). Following amniocentesis, T_3 (40 μg) was injected into the amniotic sac. T_3 and TSH 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.

More recently, attention has focused on the maternal administration of TRH, which, unlike thyroid hormones, crosses the placenta. Roti et al. administered TRH or saline to 214 term pregnant women at various time intervals (8–820 min) before delivery (58). Cord blood was obtained, and thyroid-pituitary function was assessed. Following administration of TRH, TSH was significantly elevated within 20 min, T_3 rose significantly by 60 min, and T_4 rose significantly by 120 min. The findings demonstrated that in the human, first, TRH crosses the placenta, second, the term fetal pituitary is responsive to TRH, and third, endogenous TSH stimulates the fetal thyroid. Supportive evidence for this work was presented by Moya et al., who administered TRH (400 or 600 μg) or saline intravenously to 26 pregnant women at term 2–12 h before elective cesarean section (59). They reported that 400 μg of TRH resulted in significant elevation of maternal and fetal TSH if administered 2 h before delivery. Fetal T_3 also increased significantly, but maternal T_3 remained unchanged.

Limitations of previous studies

Despite the value of information gained from animal work, the interpretation and extrapolation of such work into the human situation should be undertaken with care, particularly as it is well recognized that there are large species and tissue differences with regard to pituitary-thyroid function.

In the human, treatment of mothers with T_3 or T_4 required large doses to increase fetal thyroid hormone concentrations and caused hyperthyroidism in the mother. Administration of T_3 or T_4 by amniocentesis entails the risk of causing premature labor as a result of the invasive technique, precisely the event that the clinician would be hoping to avoid. Furthermore, in cases of severe growth retardation or premature membrane rupture, amniotic fluid volume may be severely reduced, and, therefore, the procedure may be technically very difficult.

Maternal administration of TRH appears to be the best method, but all current studies in humans have been confined to pregnancies at term, and the data may not be applicable to the earlier gestations of 24–34 weeks, when the infants are at most risk of RDS.

THYROID FUNCTION IN NORMAL FETUSES

Although the early studies have been helpful in improving our understanding of early thyroid function, they provide conflicting results, probably because of the method of sample collection, and it is possible that the results may not truly reflect undisturbed fetal thyroid activity. We have used blood samples obtained at cordocentesis to establish reference ranges of fetal TSH, TBG, and thyroid hormones in normal human fetuses and to examine the interrelationships of these hormones at 12–37 weeks gestation.

Patients and methods

Blood was obtained from 62 fetuses by cordocentesis (17–37 weeks of gestation) or cardiocentesis (<14 weeks gestation) as previously described (38). Maternal blood was collected in 52 cases from the antecubital fossa immediately before fetal blood sampling. The indications for cordocentesis (n = 58) were (a) prenatal diagnosis of blood disorders, such as hemophilia A (n = 9), (b) fetal karyotyping for women of advanced maternal age who booked late or in whom amniocyte culture had failed or a low maternal serum alpha-fetoprotein had suggested a significant risk of chromosomal defect (n = 14), (c) karyotyping for fetal malformations, such as mild hydronephrosis, unilateral multicystic kidney, or congenital diaphragmatic hernia (n = 24), (d) investigation of maternal primary toxoplasmosis (n = 2), and (e) fetal blood grouping in red cell-isoimmunized pregnancies in which the fetal blood was subsequently found to be Coombs' test negative (n = 9). In all cases, the fetal abdominal circumference and blood gases at the time of cordocentesis were within our reference ranges for gestation, and the fetal karyotype was normal. Furthermore, the fetuses did not have the

blood disorder or infection for which they were investigated. Blood was obtained from 4 fetuses by cardiocentesis immediately before intracardiac injection of potassium chloride for fetocide in multifetal pregnancies. Kleihauer-Beteke testing confirmed that all samples contained only fetal blood.

For measurements of serum TSH, thyroxsine-binding globulin (TBG) and thyroid hormones, fetal (0.3–0.8 mL) and maternal (5 mL) blood samples were collected into plain tubes and centrifuged for 10 min at 2000 rpm, and the serum was collected and stored at −20°C. TSH was measured in all, and total T_4 (TT_4), free T_4 (FT_4), total triiodothyronine (TT_3), free T_3 (FT_3), and TBG were measured in most fetal serum samples (60).

Results

The results of the measurements of TSH, free and total T_4 and T_3, and TBG concentrations in fetal and maternal serum are shown in Figures 1, 2, 3, and 4. Fetal serum TSH, total and free T_4 and T_3, and TBG concentrations increased progressively during gestation, and the associations between each of them and gestational age were significant.

Although there were also significant associations between these variables, multiple regression analysis demonstrated that the only significant association independent of gestation was that between serum TSH and FT_4 [$FT_4 = -1.0873 + 0.768$ (TSH) + 0.042 (gestational weeks); $R = 0.896$, $p < 0.0001$].

There were no changes in maternal hormone or TBG concentrations as a function of gestation age (Figs. 1, 2, 3, 4). Likewise, there were no significant associations between the values in maternal serum and those in fetal serum. Most fetal serum TSH values were higher, whereas most fetal serum total and free T_3 values were lower than the respective adult values. The fetal serum TT_4, FT_4, and TBG values reached the respective mean adult values at approximately 36 weeks gestation.

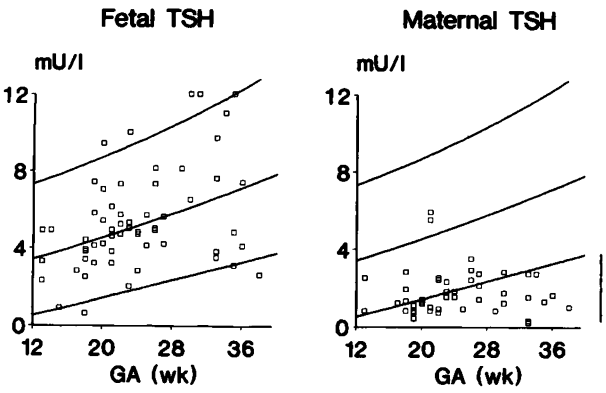

FIG. 1. The individual fetal and maternal values of serum TSH concentration in normal fetuses and fetal reference range (mean, 5th and 95th percentiles) with gestational age. The vertical line at right is the normal nonpregnant adult range (mean 2.9, range 0.4–5.5 mU/L). (From ref. 60.)

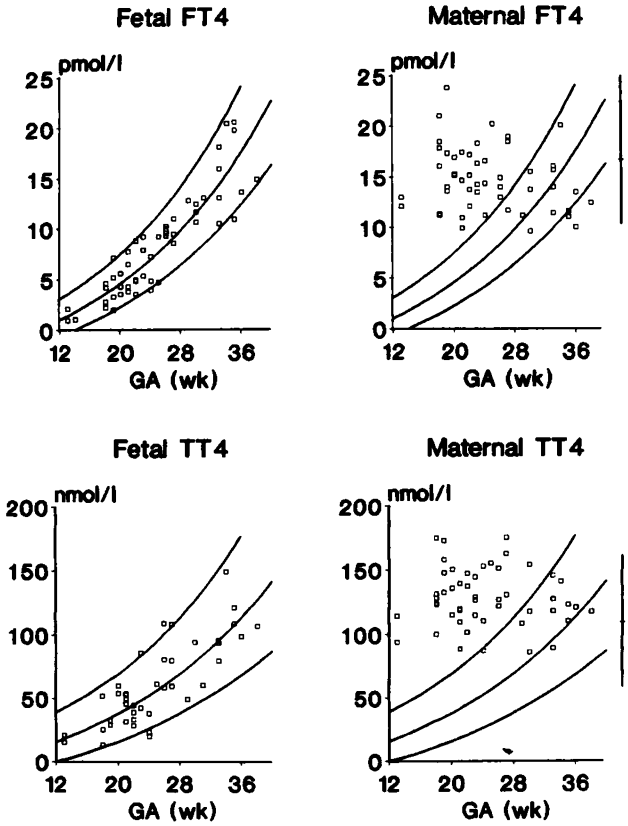

FIG. 2. The individual fetal and maternal values of serum free T_4 (FT_4) and total T_4 (TT_4) concentrations in normal fetuses and fetal reference range (mean, 5th, and 95th percentiles) with gestational age. The vertical lines at right are the normal nonpregnant adult ranges (FT_4: mean 18 pmol/L, range 10.3–25.7 pmol/L; TT_4: mean 109 nmol/L, range 58–161 nmol/L). (From ref. 60.)

Discussion

The maternal serum levels of total thyroid hormones are higher than those of nonpregnant adults. The increase in TT_4 is primarily a consequence of estrogen-induced elevation of serum TBG and, to a lesser extent, the mild TSH-like activity of human chorionic gonadotrophin (61–63). Although in the present study the maternal levels did not change significantly with gestation, in a larger series, Fung et al. reported that the levels of FT_4 and FT_3 decrease with gestation (64). The absence of significant correlation between fetal and maternal thyroid hormones and TSH levels is compatible with previous studies that measured thyroid hormones in cord blood samples at delivery (10). Thus, whereas in other species, such as the rat, maternal thyroid hormones play an important role in fetal life (62), in the human fetus, the pituitary-thyroid axis seems to develop independently from that of the mother.

Both the bound and free fetal thyroid hormone concentrations increase with advancing gestation. However, although fetal TT_4 and FT_4 concentrations reached adult levels by 36 weeks gestation, the fetal TT_3 and FT_3 concentrations were always less than half the respective mean adult concentrations. Since the major source of FT_3 is peripheral conversion of T_4, these findings suggest that in intrauterine life the processes necessary for this conversion are either immature or lack the necessary stimulus for their activation. In vitro studies in sheep have

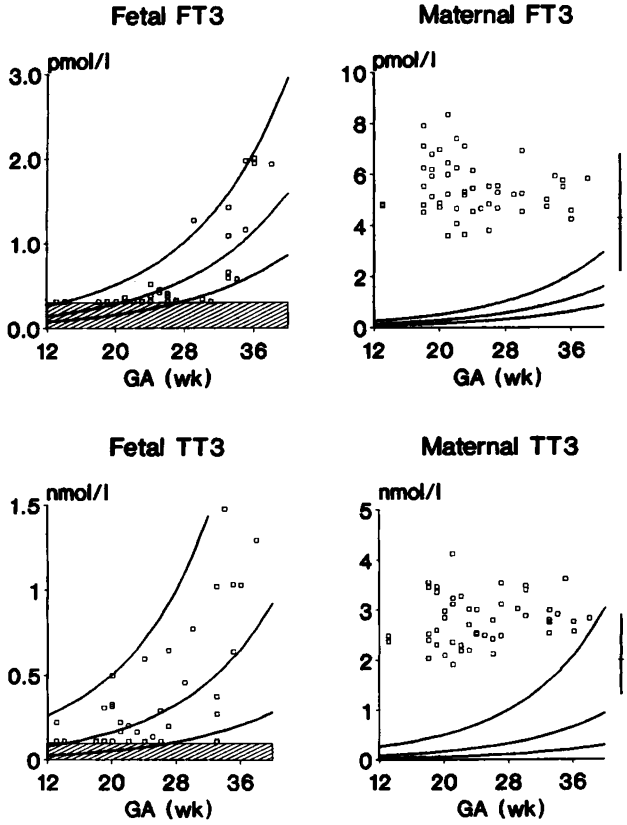

FIG. 3. The individual fetal and maternal values of serum free T_3 (FT_3) and total T_3 (TT_3) concentrations in normal fetuses and fetal reference range (mean, 5th, and 95th percentiles) with gestational age. The vertical lines at right are the normal nonpregnant adult ranges (FT_3: mean 4.5 pmol/L, range 2.2–6.8 pmol/L; TT_3: mean 2.1 nmol/L, range 1.3–2.9 nmol/L). Hatched areas represent the lower limits of sensitivity for the assays. (From ref. 60)

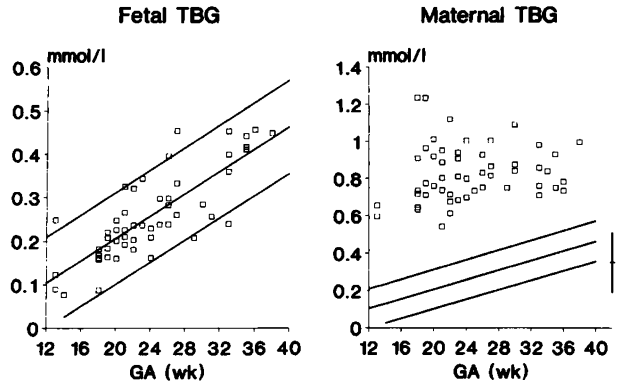

FIG. 4. The individual fetal and maternal values of serum TBG concentration in normal fetuses and fetal reference range (mean, 5th, and 95th percentiles) with gestational age. The vertical line at right is the normal nonpregnant adult range (mean 0.35 μmol/L, range 0.19–0.51 μmol/L). (From ref. 60.)

demonstrated 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 (65). Similarly, Fisher et al. 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 (10). An alternative explanation for the low fetal T_3 concentrations could be rapid deiodination by the placenta.

The increase in the fetal thyroid hormone concentrations with gestation presumably 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 independent 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 study by Vulsma et al. of infants with severe congenital hypothyroidism suggested that a substantial amount of T_4 is transferred from mother to fetus (66), 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. This study was performed in hypothyroid fetuses and infants, and its relevance to normal fetuses may be questioned.

Fetal serum TSH increases significantly with gestation, and the concentration is always higher than in the mother. In postnatal life, the major determinant of negative feedback is intrapituitary T_3, originating from the local monodeiodination of T_4 (67). In the present study, there was a gestational age-independent positive association between FT_4 and TSH, and even in the third trimester when adult concentrations of TT_4 and FT_4 were reached, TSH concentration continued to rise. These findings suggest that the fetal pituitary is relatively insensitive to negative feedback from thyroid hormones. Alternatively, in the fetus, circulating FT_3 has a more important role in feedback than in the adult. Since in the fetus the concentration of FT_3 is much lower than in postnatal life, the threshold for negative feedback is never reached in utero. Therefore, the high TSH concentration may be a consequence of fetal pituitary hyperactivity in the presence of a hypothyroid intrauterine environment.

Fetal serum TBG concentration increases with gestation and reaches adult levels during the third trimester. This probably reflects the functional maturation of the fetal liver and its increasing capacity to manufacture proteins. Fetal albumin concentration also increases with gestation (68). 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.

The data of the present study support the findings of Greenberg et al. that TSH, TT_4, and FT_4 increase between 11 and 24 weeks gestation (25). However adult levels are not reached by 16–20 weeks as they reported, and our data do not support the notion that TSH secretion is responsive to FT_4 from as early as the 11th week of gestation. Similarly, although our data on thyroid hormone concentrations arein general agreement with those of Fisher et al. (10), we did not confirm their finding that fetal TSH rises between 12 and 24 weeks but not thereafter. The present data agree most closely with those of Ballabio et al. (29), who also obtained blood by cordocentesis and similarly demonstrated pituitary insensitivity to circulating TT_4 and FT_4.

During the second trimester of pregnancy, it is likely that the increase in fetal blood TSH, thyroid hormones, and TBG represents independent and autonomous maturation of the pitu-

itary, 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 TT_3 and FT_3 are always lower than in postnatal life, and in intrauterine life, there is uninhibited production of TSH. The increase in fetal serum TSH, TBG, total and free T_4 and T_3 with gestation reflects increasing maturation of the pituitary, thyroid, and liver. 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.

NORMAL FETAL RESPONSE TO MATERNAL TRH

In the prevention of RDS, the limitations arising from the use of corticosteroids have stimulated the search for alternative methods. There is substantial evidence that thyroid hormones play a major role in pulmonary development, and animal studies have demonstrated improvement in fetal pulmonary maturation after maternal administration of TRH or intraamniotic or direct fetal injection of T_3 or T_4. The present study was designed to investigate whether maternal TRH, administered earlier in gestation than previously studied, could also stimulate the fetal pituitary.

Patients and methods

Serum TSH was measured by radioimmunoassay in maternal and umbilical venous blood samples obtained immediately before and after fetal blood transfusion by cordocentesis, in 26 red cell-isoimmunized pregnancies at 25–37 weeks gestation. In 8 cases, immediately after obtaining the pretransfusion fetal blood sample, TRH (200 μg, Roche Ltd, Welwyn Garden City, England) was given intravenously to the mothers (69).

Results

In the maternal group that received TRH, the mean TSH concentration in the posttransfusion fetal samples was significantly higher than before the transfusion (Fig. 5). The percentage increase in fetal TSH concentration (mean 420%, range 140%–890%) was significantly related to the interval between TRH administration and posttransfusion sampling. The increase in fetal TSH also was significantly related to the time interval between the administration of TRH and the collection of the posttransfusion samples (Fig. 5) but not to gestational age at transfusion, the change in fetal hemoglobin concentration, the rate of transfusion, or expansion of the fetoplacental blood volume. In the control fetal group, there were no significant differences between the pretransfusion and posttransfusion TSH concentrations in the fetal blood (Fig. 5).

In the maternal group that received TRH, the mean TSH concentration in the posttransfusion maternal samples was significantly higher than before the transfuion (Fig. 5). In the control group, there were no significant differences between the pretransfusion and posttransfusion TSH concentrations in the maternal blood.

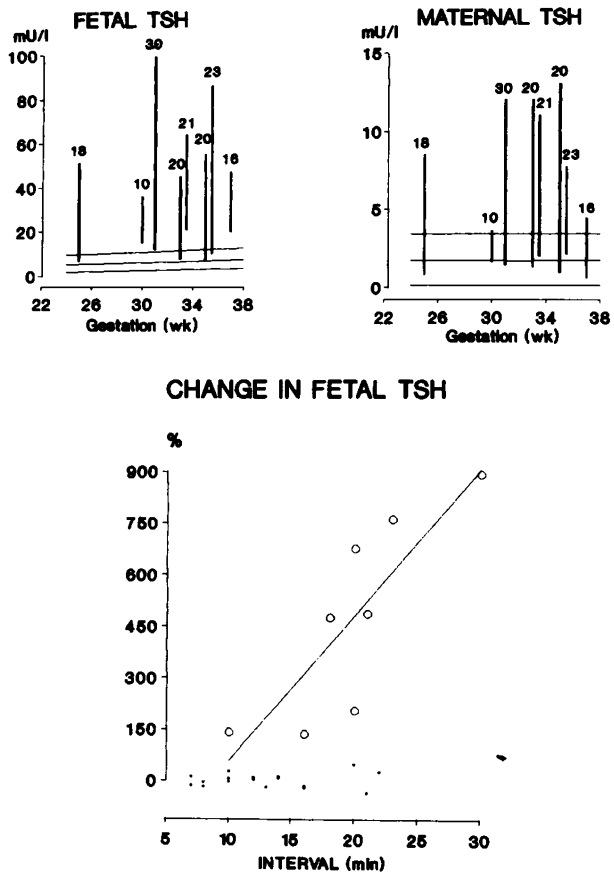

FIG. 5. Increase in fetal and maternal blood concentration of TSH (mU/L) within 10–30 min of administration of TRH to the mother (actual time interval given above TSH response in each case), plotted on the appropriate reference range (mean, 5th, and 95th percentiles) for gestation (**top**). The change in fetal TSH is significantly related to the time interval from the administration of TRH to the mother (○). In the control fetuses (●), there was no significant difference between pretransfusion and posttransfusion TSH concentrations. (From ref. 69.)

Discussion

Fetal blood transfusion does not change the fetal TSH concentration. However, maternal administration of TRH is associated with a rapid increase in fetal TSH. Since the magnitude of the fetal response is similar to that reported in fetuses undergoing TRH stimulation at term (49,50), the data of the present study suggest that fetal pituitary responsiveness is established from at least 25 weeks gestation. Furthermore, 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.

In pregnancies at term, maternal administration of TRH was associated with increased T_3 concentrations in cord blood at delivery (58,59). However, the minimum inerval for this response was 40–60 min. Therefore, in our study, due to the relatively short interval between obtaining the pretransfusion and post transfusion samples, thyroid hormones were not assayed. It was thought unlikely that any significant changes

would be detected. Indeed, the ability of the fetal thyroid gland to respond to an increased TSH stimulus is open to question. Data on the normal fetuses have suggested that the fetal thyroid gland is relatively unresponsive to the already high TSH concentrations found in utero and appears to mature independent of the pituitary gland.

Nevertheless, if TRH is to be used for the stimulation of fetal lung maturation, it need not necessarily have to produce an increase in fetal thyroid hormones. Thus, Morales et al. demonstrated in a randomized study (70) that although the combined use of corticosteroids and TRH would enhance fetal lung maturation to a greater degree than would corticosteroids alone, cord blood levels of thyroid hormones were not significantly different between the two groups.

Maternal administration of TRH is able to stimulate the fetal pituitary gland to produce TSH. The response is rapid, dramatic, and unrelated to gestational age. Further study is required to more closely define the time course of the response, optimal TRH dosage, and possible changes in thyroid hormone levels. 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 (71). The relevance of such studies to the human fetus must be interpreted with care. Prospective controlled trials will be required to assess the value of this treatment, either alone or in addition to glucocorticoids, as a method of enhancing fetal lung maturation, but the quick response time suggests that TRH would be a useful adjuvant to current attempts at preventing or reducing the consequences of RDS.

THYROID FUNCTION IN SMALL-FOR-GESTATIONAL-AGE (SGA) FETUSES

In postnatal life, illness and malnutrition influence every aspect of thyroid activity, including control of secretion, transport, metabolism, and ultimate action of the thyroid hormones. This is considered to be a beneficial adaptation, with consequent decrease in caloric expenditure and conservation of essential proteins (17,72–74).

In intrauterine life, investigation of fetal blood samples obtained by cordocentesis has demonstrated that some SGA fetuses are chronically starved, as documented by fetal hypoxemia, hyperlacticemia, acidemia, and deranged carbohydrate, lipid, and amino acid metabolism (39,40). We investigated possible changes in thyroid function in intrauterine malnutrition.

Patients and methods

Thyroid function was studied in umbilical venous blood samples obtained by cordocentesis at 22–38 weeks gestation from 49 women referred for fetal karyotyping and blood gas analysis because of ultrasonographic evidence of severe fetal growth retardation (the fetal abdominal circumference was 2–11 SDs below the normal mean for gestation). All fetuses were morphologically and chromosomally normal (75).

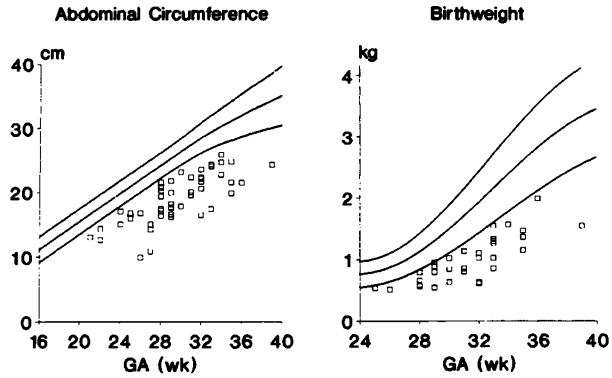

FIG. 6. The individual abdominal circumference (**left**) and birthweight (**right**) measurements in 49 SGA fetuses, plotted on the normal reference ranges (mean, 5th, and 95th percentiles) for gestation. (From ref. 75.)

Results

The fetal abdominal circumference was significantly reduced (2–11 SDs below the expected mean for gestation), and the head/abdominal circumference was significantly above the expected mean for gestation. The individual values are plotted on the appropriate reference ranges (mean, 5th, and 95th percentiles) for gestation in Figure 6. The SGA fetuses had significantly lower Po_2 and pH values than the normal group.

The SGA fetuses had significantly higher TSH (Fig. 7) and lower TT_4 and FT_4 (Fig. 8) than did the normal group. Fetal TT_3, FT_3, and TBG were not significantly different between SGA and normal fetuses. In the growth retarded fetuses, there

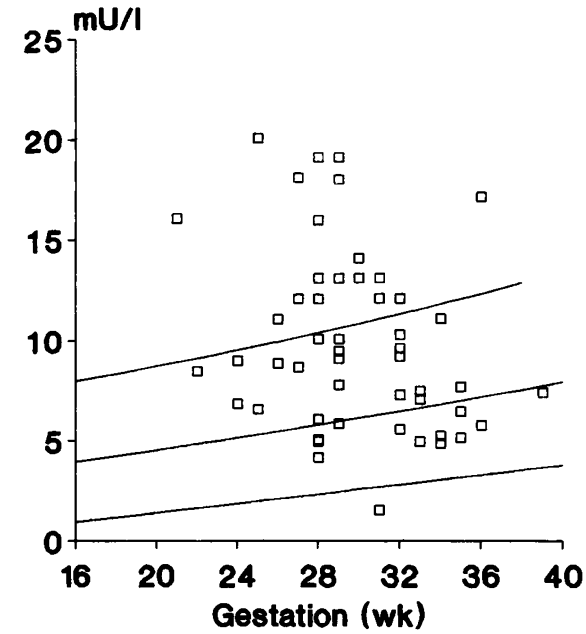

FIG. 7. The individual values of serum TSH concentration in 49 SGA fetuses plotted on the appropriate reference range (mean, 5th, and 95th percentiles) for gestation. (From ref. 75.)

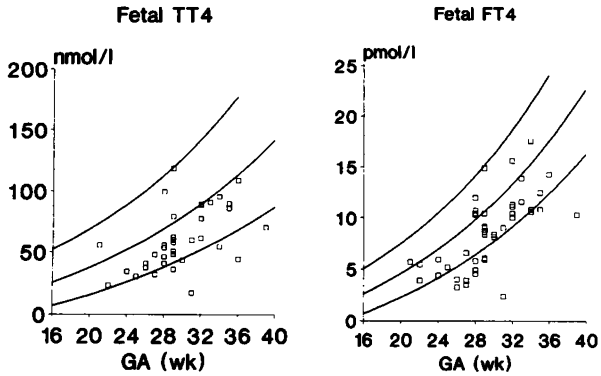

FIG. 8. The individual values of serum TT_4 concentration (**left**) (n = 36) and FT_4 (**right**) (n = 45) in SGA fetuses plotted on the appropriate reference range (mean, 5th, and 95th percentiles) for gestation. (From ref. 75.)

were significant associations between fetal delta TSH and delta Po_2 and between fetal delta FT_4 and delta pH.

Discussion

In SGA fetuses, TSH is higher and thyroid hormones are lower than in normal fetuses. Furthermore, the magnitude of the observed derangement in the pituitary-thyroid axis is related to the degree of fetal hypoxemia and acidemia. Since the cause of growth retardation in some SGA fetuses is impaired placental perfusion and chronic starvation, our data provide evidence that, as in postnatal life, intrauterine hypothyroidism may represent a beneficial adaptation to starvation, with a consequent decrease in metabolic rate and oxygen consumption. However, in postnatal starvation, serum TSH is usually normal or low and the response to TRH is blunted (76,77). Therefore, the high concentration of TSH observed in SGA fetuses suggests that the low concentration of thyroid hormones does not constitute a purposeful adaptive mechanism in the face of a hostile intrauterine environment. Reduced synthesis of thyroid hormones may be due to either impaired placental perfusion and consequent reduction in the supply of essential nutrients or hypoxic suppression of thyroid function. Alternatively, since in normal fetuses there is a gestation-related maturation of the thyroid gland (10), the low thyroid hormone concentration in some SGA fetuses may be due to developmental delay.

Irrespective of the underlying cause, the reduction in serum thyroid hormone concentration may adversely affect the fetus. Thyroid hormones have been attributed a wide range of important physiologic functions. In amphibians, thyroid hormones are essential for growth and maturation, and hypothyroidism in sheep and monkeys is associated with growth retardation (10,78–81). Animal studies, mainly in rats, have suggested that thyroid hormones have a critical role in the growth and functional development of the brain (2,62). Thus, the development of different regions in the brain follows a genetically determined time frame, and in thyroidectomized animals, there are developmental delay and neurologic deficits. Although these abnormalities may be corrected by subsequent administration of thyroxine, brain damage may become irreversible if hormone supplementation is not provided within certain critical periods of development (82). Similarly in the human, untreated congenital hypothyroidism is associated with marked abnormalities in physical and neurologic development, manifested at its extreme by cretinism. Although in congenital hypothyroidism prompt therapy in the postnatal period usually prevents these adverse sequelae (83), early onset intrauterine hypothyroidism, as documented in some SGA fetuses, could result in irreversible brain damage and may be one of the underlying causes of mental handicap in such infants.

The high concentration of TSH in SGA fetuses may be a consequence of the reduced levels of thyroid hormones, and there is evidence from both animal and human studies to support T_4 feedback control in fetuses from midgestation (84). However, there were no significant associations between delta TSH and delta TT_4 or delta FT_4. Furthermore, the data from our normal fetuses suggest that in intrauterine life the fetal pituitary gland is not susceptible to feedback from thyroid hormones. An alternative explanation for the increased TSH in SGA fetuses is pituitary hyperactivity in response to the altered metabolic milieu in some of these fetuses. Supportive evidence for this is provided by the significant association between delta TSH and the degree of fetal hypoxemia. Catecholamines may regulate secretion of TSH from the pituitary gland in the fetus (85), and Greenough et al. have reported that the concentration of norepinephrine in fetal blood obtained by cordocentesis is significantly higher in hypoxemic SGA fetuses than in normal controls (86).

A third possible explanation for the apparent pituitary hyperactivity in some SGA fetuses is increased brain perfusion. Both animal experiments and, more recently, human studies with Doppler ultrasonography (87,88) have documented that in fetal hypoxemia there is redistribution in fetal blood flow in favor of the brain and at the expense of the viscera. It could be postulated that thyroid hormone deficiency is the result of thyroid gland underperfusion, whereas the high TSH is due to increased brain perfusion.

This study demonstrated that some SGA fetuses may have abnormal thyroid function and provides further evidence of the deranged metabolic and endocrine status of this group of fetuses. The low thyroid hormone concentrations could result in beneficial reduction of caloric expenditure and prolong survival in the presence of a hostile intrauterine environment. However, prolonged fetal hypothyroidism could have an adverse effect on brain development.

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