Perinatal Thyroid Physiology and Disease

Edited by

Delbert A. Fisher
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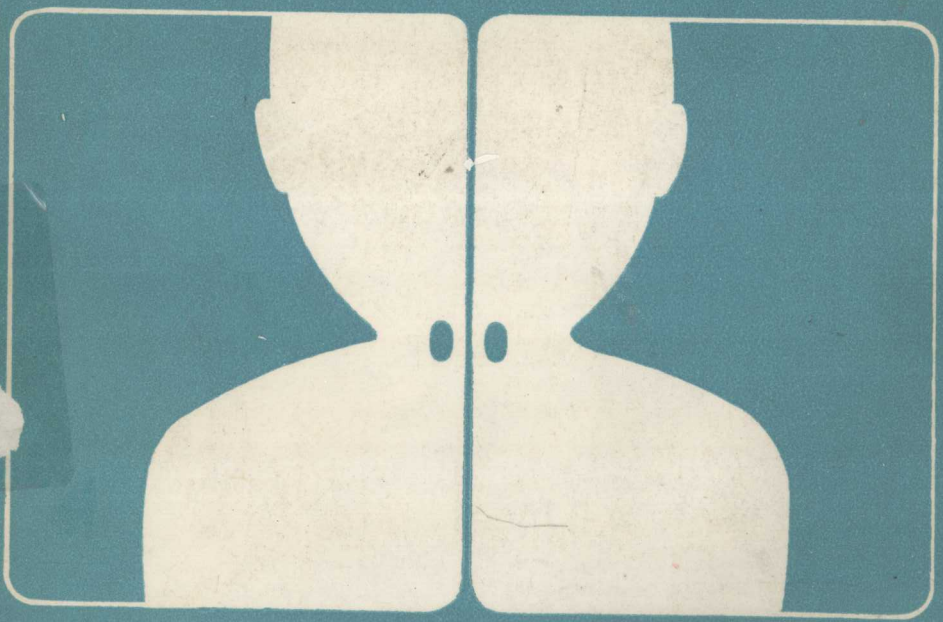

Perinatal Thyroid Physiology and Disease

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Preface

Thyroid hormones play a crucial role in the development of the organism, perhaps most strikingly evidenced by metamorphosis of the tadpole. Although the role of thyroid hormones is not quite as remarkable in mammals, thyroid deficiency at critical periods of human development may severely limit somatic growth and central nervous system maturation. Although it has been known for the past century that congenital hypothyroidism or cretinism is caused by a lack of thyroid hormones during a crucial period of development, very little progress has been made in the early diagnosis and treatment of this disorder, the etiology of which is also unknown. Moreover, there is a paucity of data as to whether early thyroid hormone treatment will prevent mental retardation. Because congenital hypothyroidism may occur as frequently as 1 in 5,000 to 1 in 10,000 births, the answer to this question is of extreme importance to the patient, to the suffering parents, and to society, who must support the retarded child.

The diagnosis, successful treatment, and possible prevention of congenital hypothyroidism requires that we fully understand normal thyroid physiology in both the mother and the fetus. This understanding is made more difficult because pregnancy imposes restraints on diagnostic procedures such as the use of radioisotopes or fetal blood sampling. Furthermore, changes in a number of parameters of thyroid function take place in both the mother and fetus during normal pregnancy. Since the human fetus does not produce thyroxine until the third month of gestation, any thyroid hormone necessary for early fetal development must come from the mother. Moreover, any thyroid hormone to be supplied by the mother would have to reach the fetus across the placental barrier. It has been very difficult to obtain data on the placental transfer of thyroid hormone during human pregnancy, but the available information from human and animal studies indicates that there is minimal transfer of thyroid hormones either from mother to fetus or from fetus to mother. Thus the fact that the infants of myxedematous mothers develop normally would suggest that, in fact, the human fetus does not require thyroid hormone for early intrauterine growth and development. In addition, because the athyroid human newborn does not manifest growth retardation, it is likely that fetal somatic growth is not dependent on thyroid hormone during late gestation.

The child with congenital hypothyroidism may appear to be euthyroid at birth, only gradually developing the clinical picture of cretinism. All in-

vestigators are unanimous in the belief that thyroid hormone therapy must be started as early as possible if mental retardation is to be avoided; since it has become clear that placental transfer of thyroid hormones is markedly limited, early neonatal screening for hypothyroidism has been recommended. Current studies indicate that this technique is both feasible and practical. Whether the early treatment of congenital hypothyroidism made possible by this screening procedure will result in normal mental development can only be answered by collecting sufficient data. If mental retardation cannot be prevented by early treatment with thyroid hormone in the neonatal period, then fetal diagnosis and treatment might be possible. Studies are being conducted to determine whether amniotic fluid might be useful in the diagnosis of fetal thyroid status and whether thyroid hormones might be administered to the fetus via amniotic fluid injection. If congenital hypothyroidism can only be successfully treated *in utero*, then we face the difficult problem of deciding which pregnant women to screen.

Considering these and other exciting advances in many areas of perinatal thyroid physiology, the editors have compiled this volume in an attempt to crystallize the problems and to better define areas of needed research. The confluence and congruence of pediatricians, internists, obstetricians, neurologists, and nutritionists interested in perinatal thyroid problems might provide new directions and dimensions. As might be expected, this volume raises more questions than it answers. However, the contributors are encouraged in the knowledge that we are on the threshold of a new era of understanding, diagnosis, and treatment of congenital hypothyroidism.

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Contents

Thyroid Disease in Pregnancy and the Newborn

Newborn Screening for Hypothyroidism

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The Hypothalamic-Pituitary-Thyroid Axis in Normal Pregnancy

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Despite numerous studies of thyroid function in pregnant women, the question whether the normal woman remains completely euthyroid during pregnancy is still unresolved. Early studies indicated that the basal metabolic rate (BMR) was elevated in pregnancy and supported the clinical impression that thyroid function was increased during pregnancy. Subsequent careful studies by Burwell (1954) indicated that the uterus and its contents could account for about 80% of the 20% rise above nonpregnant levels, and that the rest of the increase was accounted for by increased work of the maternal heart. The impression that thyroid function might be increased in the pregnant woman was reinforced by the discovery that the serum protein-bound iodine (PBI) concentration was increased during pregnancy (Heinemann, Johnson, and Man, 1948). Subsequent work indicated that this increase in serum thyroxine (T4) was caused by increases in thyroxine-binding globulin (TBG) (Dowling, Freinkel, and Ingbar, 1956).

Whether the increased TBG in pregnancy affects the amount of thyroid hormone available for metabolic activity is unclear. Theoretically the increase in thyroid hormone bound to the TBG is balanced by a decrease in T4 turnover and the amount of free or metabolically active hormone remains the same. Engbring and Engstrom (1959) administered estrogens to athyreotic patients receiving adequate thyroid hormone, which resulted in an elevation of the serum PBI determination. When estrogens were administered to patients on inadequate thyroid hormone replacement, there was no increase in the serum PBI determination. However, the amount of thyroid hormone given to these patients was not specified.

Presumably after free thyroid hormone enters the cell and exerts its physiologic action, the hormone is metabolized. Dowling, Freinkel, and Ingbar (1960) found a decrease in the fractional rate of T4 turnover when TBG capacity was increased by estrogen administration. They suggested that T4 binding by TBG exerts a rate-limiting effect on the peripheral metabolism of thyroid hormone. The absolute rate of thyroid hormone degradation was unchanged because there was a corresponding increase in total serum T4 concentration. Dowling, Appleton, and Nicoloff (1967)

found that net T4 turnover and thyroid hormone requirements were unchanged during normal human pregnancy. Net T4 turnover was 90 μg per day in the nonpregnant group and 97 μg per day in the pregnant group. The two values were identical when expressed as daily turnover per square meter of body surface.

Suggestions that thyroid function might be increased in the normal pregnant woman were also reinforced by the increased prevalence of goiter in pregnancy and an increased thyroidal radioactive iodine uptake (Halnan, 1958; Crooks, Tulloch, Turnbull, and Hytten, 1964). The increased prevalence of goiter has been explained by a relative iodine deficiency caused by increased urinary iodide clearance, which might also explain the increased radioactive iodine uptake in the thyroid. Despite plausible explanations for the changes in the thyroid function during pregnancy, the impression remained that thyroid function might be increased; this impression was heightened by the clinical picture of tachycardia, nervousness, and diaphoresis not uncommonly seen in the normal pregnant woman.

Furthermore baseline thyroid-stimulating hormone (TSH) values have also been reported to be slightly increased during the early part of pregnancy but return to normal by term (Malkasian and Mayberry, 1970). Pregnant women had a mean TSH value of 12.8 μU/ml in the first trimester compared to a mean value in euthyroid nonpregnant females of 8.3 μU/ml. Hennen, Pierce, and Freychet (1969) found an increase in thyrotropin as determined by bioassay in the serum of pregnant women. The thyroid-stimulating activity in the serum of pregnant women was comparable to that found in the serum of patients with primary myxedema. In one patient the serum had the characteristics of human chorionic thyrotropin in the radioimmunoassay. Other workers have been unable to find marked increases in bioassayable thyrotropin in normal pregnancy (Hershman and Hershman, 1972; Hershman, Kojima, and Friesen, 1973). Recently, the question had been raised as to whether the thyroid stimulator found in the serum and tumor of patients with trophoblastic disease and hyperthyroidism might be human chorionic gonadotropin (HCG). However, HCG is not thought to be the stimulator that has been found in normal placentas. The alpha subunit of TSH and HCG is identical, and it is the beta subunit that confers specificity.

Although the serum T4 concentration is increased during pregnancy concomitantly with the increase in TBG, the free T4 concentration in pregnant women has been reported to be normal or slightly low (Burrow, 1972). Whether the determination is sufficiently sensitive to measure small differences that might reflect real but minimal increases in thyroid function is not clear. Furthermore, previous work has virtually ignored serum triiodothyronine (T3) concentrations, which have now been shown to play a major role in thyroid hormone economy (Braverman, Ingbar, and Sterling, 1970). Serum T3 concentrations have been demonstrated to rise during pregnancy in a manner similar to serum thyroxine. However, we know of no

data on serum free-T3 concentration in pregnancy, and these levels may be the major determinant of thyroid hormone action.

Determination of serum free thyroid hormone concentrations alone may not be a sufficiently accurate indicator of thyroid function. Recently, evidence has accumulated to indicate that thyroid hormone acts by binding to nuclear receptors in a manner analogous to steroids. Free plasma cortisol concentrations are clearly elevated during pregnancy and could be expected to lead to the production of Cushing's syndrome during gestation. However, serum progesterone levels are also increased and apparently bind to receptors but do not initiate glucocorticoid action. Therefore the increased free plasma cortisol may be necessary to ensure normal glucocorticoid effects in the face of increased progesterone levels (Baxter and Forsham, 1971). A similar process could occur with circulating thyroid hormone. The evaluation of some physiologic action of thyroid hormone would be advantageous in determining thyroid function during pregnancy.

One such approach involves the TSH response to thyrotropin-releasing hormone (TRH). Minimal changes in free thyroid hormone are reflected in modified TSH responses to TRH. Presumably these changes reflect the concentration of thyroid hormone that binds to pituitary nuclear receptors. Accordingly the TSH response to TRH was determined in pregnant women between the 6th and 20th week of gestation after TRH infusion immediately prior to therapeutic abortion. The details of the study were discussed with each patient and all subjects gave informed written consent.

Synthetic TRH was administered through an indwelling venous catheter as a bolus injection of 100 or 500 μg. Blood samples were collected through the same catheter at time -15, 0, $+15$, $+30$, $+45$, $+60$, $+90$, and $+120$ min for TSH determinations. Nausea and or facial flushing, occurring approximately 1 min postinjection and lasting for several minutes, was observed in 10 of 19 pregnant patients. Five of the pregnant patients expressed an urge to micturate. Five nonpregnant women and five nonpregnant women taking oral contraceptives for more than 3 months were also studied as controls. No attempt was made to study each control patient in the same phase of the menstrual cycle.

Baseline blood specimens on all subjects were analyzed for total thyroxine displacement [T4(D)] and for erythrocyte T3 uptake (ET3U). Free serum T4 concentrations were determined in four patients receiving 500 μg of TRH. Serum T4 concentrations were determined by displacement analysis as described by Seligson and Seligson (1972). Serum ET3U was calculated by comparing the uptake of T3 by patient's serum to a normal serum pool, which was assigned a value of 100. Free T4 levels were measured by the method of Oppenheimer, Sove, Surks, and Hauer (1963). The serum TSH levels were determined in our laboratory by the double antibody radioimmunoassay technique described by Odell, Wilbur, and Paul (1965). The TSH for iodination and the thyrotropin antiserum were obtained

from the National Institutes of Health; the TSH standard (TSH 68/58) was obtained from the National Institute for Medical Research, London. All the samples in this study were analyzed in the same TSH assay. Normal values in our laboratory are as follows: T4(D), 4.6 to 9.2 μg/100 ml; serum ET3U, 93 to 107%; and TSH, up to 10 μU/ml.

RESULTS

The time course of mean serum TSH concentrations in response to 100 μg of TRH is shown in Fig. 1. Each group exhibited a similar type of response curve with similar TSH values at 120 min. Patients who were 16 to 20 weeks pregnant had a greater mean TSH response at the 15-, 30-, 45-, 60-, and 90-min time intervals than did nonpregnant controls or patients 6 to 12 weeks pregnant. Patients receiving oral contraceptives showed a TSH response to TRH that was similar to the group who were 16 to 20 weeks pregnant. There was no significant difference in TSH response among women 6 to 12 weeks pregnant whether they received 100 or 500 μg of TRH.

Mean serum T4 and ET3U values are shown in Table 1. Seven of 15 patients in the 6th to 12th week of pregnancy and two of four patients 16 to 20 weeks pregnant had serum T4(D) determinations greater than 9.2 μg/100 ml, as did three of five patients receiving oral contraceptives.

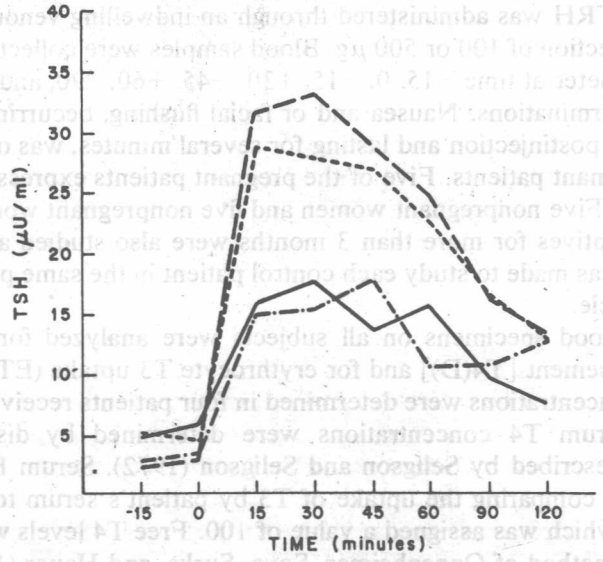

FIG. 1. TSH response to TRH in pregnant and nonpregnant women. TRH (100 μg) was injected at time zero. There were five patients in each group except for the 16 to 20 weeks pregnant group which contained four patients. (——) 6–12 weeks pregnant; (– – –) 16–20 weeks pregnant; (—·—) nonpregnant controls; (– –) nonpregnant, oral contraceptives.

TABLE 1. *Thyroid function tests in pregnant and nonpregnant women*

Test	Nonpregnant controls ($n = 5$)	Nonpregnant on oral contraceptives ($n = 5$)	6 to 12 weeks pregnant ($n = 15$)	16 to 20 weeks pregnant ($n = 4$)
Serum T4(D)[a]	6.5 ± 0.6 (5.1–8.0)	8.9 ± 0.9 (6.8–11.1)	9.1 ± 0.6 (6.5–11.6)	11.0 ± 1.5 (8.9–15.0)
ET3U[b]	101 ± 1 (98–103)	109 ± 2 (104–113)	107 ± 2 (98–117)	115 ± 1 (114–117)

Mean values ± SEM at time zero; range in parentheses.
[a] Expressed as micrograms per 100 ml.
[b] Expressed as percent.

Pregnancy and oral contraceptives also increased the ET3U to values in the hypothyroid range. Serum free T4 concentrations were determined for four patients 6 to 12 weeks pregnant who had received 500 μg of TRH and showed no consistent variation from baseline levels at 30, 60, and 90 min after TRH administration.

Kannan, Sinha, Devi, and Rastogi (1973) administered TRH to a group of 10 pregnant women during each trimester and concluded that the TSH response to TRH remained unaltered during pregnancy. However, calculations based on their data suggest that at 13 to 24 weeks of pregnancy, the mean TSH response to TRH was significantly increased as compared to controls. Hershman, et al. (1973) studied 13 pregnant women and found an augmented TSH response to 500 μg of TRH as compared to young men. However, they did not comment whether the TSH response was increased in pregnancy as compared to the nonpregnant state.

Animal studies have also shown increased responsiveness of the pituitary-thyroid axis during pregnancy. Kojima, Hershman, Azukizawa, and Di Stefano (1974) demonstrated that pituitary TSH secretion increased, the TSH response to TRH increased, and serum T3 and T4 levels decreased during pregnancy in the rat. They attributed these findings to hypothyroidism, increased peripheral disposal of thyroid hormone, or to both possibilities. The greater serum TSH response to TRH suggested enhanced sensitivity of the thyrotrope to TRH in the pregnant rat. They did not believe these changes could be due to enhanced estrogen secretion because the administration of estradiol to male rats did not effect the TSH response to TRH. Whether data in the pregnant rat can be compared to the human experience is questionable. Galton (1968) has previously demonstrated that peripheral disposal of thyroid hormone is increased in the pregnant rat, whereas this does not occur in the pregnant woman.

In the present study, there was an increased TSH response to TRH

stimulation in women between the 16th and 20th weeks of pregnancy. Since a similar increase in TSH responsiveness occurred in women receiving oral contraceptives, these findings suggested that the increased estrogen or progesterone levels in pregnancy "primed" the pituitary TSH response to TRH. Estrogens have a similar effect with other pituitary hormones. Nonpregnant women have been found to have a greater TSH response to TRH than did men in some, but not all, studies. Noel, Dimond, Wartofsky, Earl, and Frantz (1974) found small but significant increases in the TSH response of women to TRH as compared to men. When the TRH infusion was prolonged rather than given as a bolus, there was a clear differential sensitivity of the TSH response in women. Gual, Kastin, and Schally (1972) were unable to demonstrate a change in TRH responsiveness in men pretreated with estrogens. Neither were Carlson, Jacobs, and Daughaday (1973) able to demonstrate an increase in the TSH response to TRH in six normal males after 5 days of diethylstilbesterol. The failure of estrogens to augment the TSH response in males might reflect sex differences, length of estrogen treatment, or obliteration of the "priming" effect by the comparatively large doses of TRH (500 μg) given in these studies.

The physiologic significance of the increased TSH responsiveness to TRH remains to be determined. The increased TSH response to TRH in pregnancy implies that the thyroid gland would undergo greater TSH stimulation in response to a given amount of TRH. This increased TSH responsiveness is evidence against the possibility that thyroid function is increased during pregnancy. Minimal increases in thyroid hormone concentration result in a markedly decreased TSH response to TRH (Snyder and Utiger, 1972).

Conceivably, the increased TSH response to TRH in pregnancy might compensate for increased capacitance of thyroid hormone secondary to the increase in TBG. As a compensatory phenomenon, a given amount of TRH released during pregnancy would result in a greater secretion of TSH and a resulting increased release of thyroid hormone from the gland. The result of these different phenomena would be maintenance of normal thyroid function during pregnancy. This hypothesis implies that transient kinetics are important in thyroid hormone economy, but there is no clear evidence for this phenomenon.

Although the evidence is not conclusive, it suggests that thyroid function during pregnancy is normal despite perturbations in the pituitary-thyroid axis. As these perturbations appear to occur in response to increased TBG, one might speculate why this particular protein increases during gestation. Estrogens are known to result in the increased production of a number of proteins including clotting factors and lipoproteins. TBG production by the liver might increase during pregnancy as a relatively nonspecific side effect of estrogen stimulation of a hepatic genome.