Serum Growth Hormone Levels in Hypothyroid and GH-Treated Thyroidectomized Rats and Their Progenies

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CHESTER E. HENDRICH[1] AND SUSAN P. PORTERFIELD
Department of Physiology and Endocrinology, Medical College of Georgia, Augusta, Georgia 30912

Abstract. **Growth hormone (GH) was measured in the sera of control, hypothyroid (thyroidectomized [Tx]) and GH-treated Tx rats and their fetuses on Days 19, 20, 21, and 22 of gestation and in their progenies on postnatal Days 1, 5, 30, and 75. Maternal endogenous serum GH increased dramatically between the 19th and 20th days of gestation and remained elevated through the 22nd day in control rats, but was depressed significantly in Tx and GH-treated Tx rats during this period. GH was not always detected in the sera of 19-day-old fetuses. On Day 20, GH was depressed in fetuses of Tx mothers as compared with those from controls or GH-treated Tx mothers. GH was elevated in sera of fetuses from GH-treated Tx rats over fetuses of control and Tx only rats on the 22nd day of gestation. In postnatal rats, those from GH-treated mothers continued to show elevated serum GH on Day 1 as compared with those from Tx only mothers. On postnatal Days 5 and 30, progenies of Tx mothers had significantly elevated GH as compared with progenies of control mothers. At 75 days of age, the GH levels of these progenies had normalized. We have shown previously that the hormonal secretions of the pituitary-thyroid axis are badly disrupted in the progenies of Tx and GH-treated Tx mothers and that even as adults these animals have tissue (brain and liver) deficits of active thyroid hormones. Although the onset of GH secretion is mildly delayed in fetuses of Tx but not GH-treated Tx mothers, the serum GH levels of both groups of progenies are elevated during most of the neonatal period through the time of puberty. It is, therefore, concluded that GH in the absence of adequate levels of thyroid hormones is ineffective in preventing many of the learning and memory deficits induced in the progenies of Tx mothers.** [P.S.E.B.M. 1992, Vol 201]

Fetal and postnatal patterns for the development of growth hormone (GH) secretion in the rat have been described previously (1–5). The absolute value for serum GH at various ages ranges considerably. Basal serum GH levels are quite low in the 19-day fetus (1, 2, 4), rise dramatically before birth (1, 2, 4), decline to lower levels in prepubertal and pubertal rats (2–5), and rise again in the adult animal (2). Some studies do not show this higher level of basal GH secretion in the adult rat (4, 5). GH secretory patterns in the pregnant rat have also been determined (6, 7). During late pregnancy, a significant increase in both basal GH secretion and GH pulse amplitude occurs (6).

Multiple facets of the kinetics of GH secretion, its tissue receptors, and receptor binding are altered by hypothyroidism. The basal and pulsatile secretion of GH is depressed significantly soon after thyroidectomy (8–11). These effects of thyroidectomy on GH secretion are in part from a decreased response to hypothalamic growth hormone releasing-hormone (12). Also, thyroid hormones are essential for GH binding sites (13, 14) and for the binding of GH at these sites (14).

There is an interaction between GH and thyroid hormones in brain development (15), and GH treatment of euthyroid (16–18) and gestational hypothyroid rats (19–21) increases certain aspects of brain development in their progenies. Some of the learning and

[1] To whom requests for reprints should be addressed at Department of Physiology and Endocrinology, Medical College of Georgia, Augusta, GA 30912.

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memory deficits of progenies of thyroidectomized (Tx) mothers are in part alleviated by GH treatment of these Tx mothers (20). The effects of maternal GH treatment on the progeny may be mediated via alterations in placental development and function and/or the secretions of other growth factors such as insulin-like growth factors (16–18).

The rationale for the present study stems from the fact that the secretion of GH is controlled by triiodothyronine (T_3), that Phase II (17th day of gestation to birth) and Phase III (postnatal) brain development are dependent upon the hormonal secretions of the progenies, and that secretions of the pituitary-thyroid axis and tissue levels of active thyroid hormones are altered significantly in the progenies of these gestationally hypothyroid mothers (21). The need to determine basal GH secretion is further emphasized by the lack of normal brain utilization of amino acids and protein synthesis in the offspring of these Tx mothers (22). Also, the recent observations that have revealed that both the rat and human placenta transport significant amounts of thyroid hormones from either fetus to mother (23) or mother to fetus (21, 24–28) and that it is dependent upon the maternal thyroidal status (21, 23, 28) create an additional need for determining whether there are correlations between the basal GH secretory patterns and the altered metabolism and brain development deficits of the progenies of Tx and GH-treated Tx mothers.

Materials and Methods

Virgin Sprague-Dawley Holtzman rats were either radiothyroidectomized with 300 μCi of ^{131}I after being on a low iodine diet for 8 days or were maintained as controls. Tx rats were maintained with 1.0 μg of thyroxine (T_4)/100 g body wt/day sc until Day 1 of pregnancy. The morning that spermatozoa were detected in the vaginal smear was considered to be Day 1 of pregnancy. At that time, the Tx rats were divided into two groups. One group received no treatment during pregnancy and one group received 0.5 IU of porcine GH/day (supplied by the National Hormone and Pituitary Program-National Institute of Diabetes, Digestive, and Kidney Diseases) during the last 10 days of gestation. The animals were autopsied either on the 19th, 20th, 21st, or 22nd day of gestation or they were allowed to complete parturition and their progenies were autopsied at 1, 5, 30, and 75 days of age.

The Tx mothers that completed parturition were given 3.0 μg of T_4/100 g body wt/day within 12 hr after delivery and thereafter 1.5 μg of T_4/100 g body wt/day during the lactational period. Cross-fostering has been shown previously not to alleviate the developmental abnormalities induced by maternal hypothyroidism. Progenies were weaned at 22 days of age. Maternal hypothyroidism was demonstrated by measuring total serum T_4 at autopsy in pregnant rats.

All animals were autopsied between 9:00 and 11:00 AM. The mothers and 30- and 75-day-old progenies were lightly anesthetized with ether and bled from the vena cava. Fetuses were removed rapidly from the uteri and they and 1- and 5-day-old neonates were bled by decapitation. Sera from fetuses and 1- and 5-day-old neonates were pooled by litter. Maternal and 30- and 75-day-old progeny sera were kept as individual samples. Generally two and never more than three of the 30- and 75-day-old progenies were taken from a single litter. Sera were kept frozen until assayed.

Serum GH was measured by a double-antibody procedure RIA using reagents provided by Dr. A. F. Parlow through the Rat Pituitary Hormone Distribution Program, National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). The results are reported in terms of NIAMDD-rat GH-RP-1, which has a biological potency of 0.6 IU (bovine GH)/mg. All sera were assayed in duplicate in a single large assay. The statistical analyses were done according to analysis of variance which was followed up with Tukey's W-procedure (honestly significant difference procedure). Utilizing a Table U, this allows for the comparison of multiple groups that have unequal sample sizes (29). As the sera of hypophysectomized rats produces a mild response in this RIA and as this rat GH assay cross-reacts to some degree with porcine GH, appropriate standards were included that contained either sera from hypophysectomized rats or porcine GH (30).

Results

By the 21st day of gestation the Tx and GH-treated Tx mothers had significantly reduced litter sizes and had increased numbers of fetal resorptions throughout this study as compared with controls (Table I). At term, Tx mothers (gestation, 24.1 ± 0.3 days) gave birth to only 66.4% and GH-treated Tx mothers (gestation, 24.2 ± 0.3 days) gave birth to only 58.2% as many live pups as did control mothers (gestation, 22.8 ± 0.3 days). The Tx mothers had offspring survival of 46.2% and the GH-treated Tx mothers had 51.5% offspring survival as compared with controls. In the absence of adequate levels of thyroid hormones, GH treatment was of little or no value in regard to reproductive performance.

GH treatment of the Tx mother did not alleviate the fetal growth retardation induced by maternal thyroid deficiency (Table II). However, fetal growth was somewhat dissociated from placental development as only the Tx nontreated mothers had consistently decreased placental weights. Likewise, fetal liver weights were decreased significantly in the progenies of both groups of Tx mothers, whereas fetal brain weights were only mildly affected, primarily in hypothyroid only mothers.

Table I. Reproductive Performance of Control, Thyroidectomized, and GH-Treated Thyroidectomized Rats[a]

Parameter and maternal treatment	Gestational age				
	19 days	20 days	21 days	22 days	Term
Live fetuses/litter					
I. Control	13.1 ± 0.60 (11)	12.9 ± 0.55 (5)	14.1 ± 0.70 (11)	12.8 ± 0.37 (49)	13.4 ± 0.44 (52)
II. Tx	12.0 ± 0.71 (11)	11.5 ± 0.61 (5)	11.6 ± 0.51 (24)	9.9 ± 0.59 (35)	8.9 ± 0.93 (40)
III. Tx + GH	12.2 ± 0.73 (7)	11.3 ± 0.59 (5)	12.3 ± 0.30 (14)	10.2 ± 0.41 (27)	7.8 ± 0.90 (48)
Statistics	NS	NS	II < I	II & III < I	II & III < I
No. fetal resorptions/litter					(No. of pups surviving 24 hr)
I. Controls	0.44 ± 0.24	0.31 ± 0.16	0.20 ± 0.11	0.37 ± 0.10	13.2 ± 0.47
II. Tx	1.30 ± 0.48	1.21 ± 0.39	1.50 ± 0.35	2.71 ± 0.38	6.1 ± 0.92
III. Tx + GH	1.83 ± 0.45	1.44 ± 0.41	1.55 ± 0.36	1.85 ± 0.41	6.8 ± 0.84
Statistics	I < III	I < II & III	I < II & III	I < II & III	II & III < I
Maternal body wt gain					
I. Controls	111 ± 5.3	128 ± 4.7	145 ± 5.0	171 ± 6.0	181 ± 4.6
II. Tx	57 ± 4.5	69 ± 3.9	81 ± 3.9	103 ± 5.2	96 ± 4.5
III. Tx + GH	55 ± 5.5	78 ± 4.0	103 ± 5.8	131 ± 4.8	122 ± 3.7
Statistics	II & III < I	II & III < I	II & III < I	II & III < I	II & III < I

[a] Data are expressed as mean ± SE; $P < 0.05$. Numbers in parentheses are the number of litters and mothers.

Table II. Body, Brain, Liver, and Placental Weights of Fetuses of Control, Thyroidectomized, and GH-Treated Thyroidectomized Mothers[a]

Parameter and maternal treatment	Gestational age			
	19 days	20 days	21 days	22 days
Body wt (g)				
I. Control	1.5 ± 0.03 (11)	2.7 ± 0.06 (5)	4.2 ± 0.08 (11)	6.0 ± 0.06 (49)
II. Tx	1.4 ± 0.02 (11)	2.3 ± 0.04 (5)	3.5 ± 0.08 (24)	4.4 ± 0.11 (35)
III. Tx + GH	1.4 ± 0.02 (7)	2.3 ± 0.07 (5)	3.3 ± 0.14 (14)	5.0 ± 0.08 (27)
Statistics	NS	II, III < I	II, III < I	II, III < I
Brain wt (g)				
I. Control	0.13 ± 0.003	0.15 ± 0.002	0.18 ± 0.002	0.22 ± 0.003
II. Tx	0.10 ± 0.004	0.13 ± 0.003	0.15 ± 0.003	0.18 ± 0.005
III. Tx + GH	0.10 ± 0.005	0.14 ± 0.004	0.16 ± 0.004	0.20 ± 0.005
Statistics	II, III < I	NS	II < I	II < I
Liver wt (g)				
I. Controls	0.16 ± 0.009	0.23 ± 0.009	0.30 ± 0.008	0.37 ± 0.009
II. Tx	0.12 ± 0.004	0.19 ± 0.008	0.24 ± 0.009	0.29 ± 0.010
III. Tx + GH	0.11 ± 0.006	0.17 ± 0.009	0.22 ± 0.007	0.31 ± 0.008
Statistics	II, III < I	III < I	II, III < I	II, III < I
Placental wt (g)				
I. Controls	0.53 ± 0.015	0.59 ± 0.010	0.61 ± 0.010	0.64 ± 0.012
II. Tx	0.47 ± 0.011	0.48 ± 0.013	0.49 ± 0.014	0.51 ± 0.014
III. Tx + GH	0.45 ± 0.014	0.50 ± 0.014	0.55 ± 0.015	0.58 ± 0.016
Statistics	NS	II, III < I	II < I	II < I

[a] Data are expressed as mean ± SE; $P < 0.05$. The numbers in parentheses are the number of litters and mothers.

During the postnatal period of 1 through 75 days of age, "catch-up" growth was not achieved in either the offspring of Tx mothers or the male progenies of GH-treated Tx mothers (Table III). Brain weights of the surviving postnatal animals were not affected significantly by maternal hypothyroidism. However, the liver weights of these progenies of both groups of Tx mothers were generally decreased below those of control offspring through 75 days of age. The degree of maternal hypothyroidism induced in these animals was demonstrated by the fact that their serum T_4 levels ranged from 28.6% to 53.3% of controls and their serum T_3 levels ranged from 25.1% to 51.7% of control levels.

We do not report any serum GH values for 19-day fetuses because they were generally below the level of detection in our assay (Table IV). The quantity of serum used in this RIA was 25 μl or 50 μl. When two to four times this volume of serum was used from 19-day fetuses, it did not always give a positive response in this RIA and those positive responses that were obtained

Table III. Body, Brain, and Liver Weights of Progenies of Control Thyroidectomized and GH-Treated Thyroidectomized Mothers[a]

Parameter and maternal treatment	Postnatal					
	1 day	5 days	30 days		75 days (adult)	
			Female	Male	Female	Male
Body wt (g)						
I. Controls	7.3 ± 0.12 (52)	12.8 ± 0.31 (48)	124 ± 3.3 (55)	139 ± 3.7 (55)	237 ± 4.0 (32)	369 ± 6.3 (32)
II. Tx	5.5 ± 0.10 (40)	11.1 ± 0.42 (42)	104 ± 5.2 (51)	108 ± 4.7 (51)	220 ± 3.8 (31)	328 ± 6.5 (31)
III. Tx + GH	6.1 ± 0.13 (48)	11.6 ± 0.21 (40)	116 ± 5.1 (53)	120 ± 3.9 (53)	228 ± 3.2 (28)	337 ± 7.1 (28)
Statistics	II, III < I	II < I	II < I	II, III < I	II < I	II, III < I
Brain wt (g)						
I. Controls	0.31 ± 0.003	0.60 ± 0.008	1.70 ± 0.03	1.78 ± 0.02	1.94 ± 0.02	2.16 ± 0.03
II. Tx	0.26 ± 0.004	0.54 ± 0.011	1.63 ± 0.03	1.66 ± 0.03	1.84 ± 0.03	2.02 ± 0.03
III. Tx + GH	0.28 ± 0.004	0.57 ± 0.009	1.65 ± 0.02	1.67 ± 0.04	1.91 ± 0.05	2.01 ± 0.04
Statistics	II < I	NS	NS	NS	NS	NS
Liver wt						
I. Controls	0.32 ± 0.006	0.43 ± 0.007	5.10 ± 0.19	6.43 ± 0.24	10.3 ± 0.22	15.3 ± 0.37
II. Tx	0.27 ± 0.008	0.36 ± 0.009	4.45 ± 0.25	4.87 ± 0.21	8.8 ± 0.25	13.5 ± 0.39
III. Tx + GH	0.28 ± 0.004	0.40 ± 0.012	4.60 ± 0.20	5.25 ± 0.28	9.4 ± 0.30	13.1 ± 0.42
Statistics	II, III < I	II < I	II < I	II, III < I	II, III < I	II, III < I

[a] Data are expressed as mean ± SE; $P < 0.05$. The numbers in parentheses are the number of animals or litters.

Table IV. Growth Hormone Levels (ng/ml) in Sera of Control, Thyroidectomized, and GH-Treated Thyroidectomized Rats and Their Fetuses[a]

Maternal treatment	Fetal				Maternal			
	19 days	20 days	21 days	22 days	Pregnant 19 days	Pregnant 20 days	Pregnant 21 days	Pregnant 22 days
I. Controls	—	44 ± 9.2 (5)	121 ± 12.0 (11)	222 ± 10.3 (49)	22 ± 3.9 (11)	82 ± 8.3 (5)	60 ± 6.8 (22)	52 ± 5.8 (49)
II. Tx	—	15 ± 3.9 (5)	95 ± 8.1 (24)	192 ± 8.8 (35)	10 ± 2.4 (11)	29 ± 5.0 (5)	17 ± 1.4 (40)	19 ± 1.9 (41)
III. Tx + GH	—	65 ± 12.6 (5)	122 ± 10.1 (14)	276 ± 13.2 (27)	11 ± 1.6 (7)	19 ± 4.0 (5)	24 ± 3.6 (19)	23 ± 3.2 (27)
Statistics		II < I & III	NS	I & II < III	II & III < I	II & III < I	II & III < I	II & III < I

[a] Data are expressed as mean ± SE; $P < 0.05$. The numbers in parentheses are the number of litters and mothers.

were on the lowest portion of the standard curve. Therefore, the data on sera from 19-day fetuses were judged to be not reliable. By the 20th day of gestation, serum GH in the fetuses was easily detectable and increased dramatically through the 22nd day of gestation. This rise in fetal serum GH was delayed in fetuses of Tx mothers but was restored above normal in the fetuses of GH-treated Tx mothers by the 22nd day of gestation.

A similar but less dramatic increase in maternal serum GH was observed 1 day before, i.e., between the 19th and 20th days of gestation. Maternal hypothyroidism blocked this late gestational rise of GH secretion and endogenous GH secretion was suppressed as would be expected in these animals (Table IV).

The true serum GH level of the GH-treated Tx mothers is not known because they were treated with porcine GH and, although this radioimmunoassay is highly specific for rat GH, there is some cross-reaction with porcine GH. The last dose of GH was given 24 hr before sacrifice and was cleared from the maternal serum prior to this time. The administration of GH to the Tx mother obviously had an effect on their fetuses because their fetuses did not show the developmental delay in initial GH secretion as did fetuses of untreated Tx mothers (Table IV). Interestingly, the 22-day gestational fetuses of GH-treated Tx mothers had basal serum GH levels that were elevated above those of either the fetuses of untreated Tx mothers or the fetuses of control mothers (Table IV).

The early neonates, i.e., 1 and 5 day olds, showed a rapid decline in serum GH levels from the late gestation fetal levels (Table V). Maternal hypothyroidism altered more radically the postnatal than the prenatal development of GH secretion and GH treatment of the Tx rat did not correct this effect completely (Table V). The general trend observed was one of elevated serum GH in the progenies of Tx mothers up to 30 days of age. The adult progenies of the Tx mothers, in fact, normalized by 75 days of age (Table V). In addition, because parturition was delayed a full day in both the untreated Tx mothers and the GH-treated Tx mothers, these postnatal progenies were gestationally 1 day older than the control postnatal progenies.

Although gestation was extended 1 full day in both

Table V. Growth Hormone Levels (ng/ml) in Sera of Progenies of Control, Thyroidectomized, and GH-Treated Thyroidectomized Mothers

Maternal treatment	Postnatal			
	1 day	5 days	30 days	75 days (Adult)
I. Controls	58 ± 5.4 (52)	10 ± 2.9 (48)	7 ± 1.6 (110)	38 ± 5.0 (64)
II. Tx	47 ± 5.0 (40)	40 ± 3.4 (42)	20 ± 3.4 (102)	46 ± 6.6 (62)
III. Tx + GH	73 ± 6.5 (48)	37 ± 4.4 (40)	15 ± 3.9 (106)	42 ± 5.6 (56)
Statistics	II < III	I < II & III	I < II	NS

[a] Data are expressed as mean ± SE; $P < 0.05$. The numbers in parentheses are the number of animals or litters.

groups of Tx mothers, their newborns were significantly smaller (controls, 6.1 ± 0.3 g; untreated Tx, 4.9 ± 0.1 g; GH-treated Tx, 5.2 ± 0.2 g), were apparently developmentally less mature, and had undergone an alarming late fetal and early neonatal (first day of life) mortality of 40–50%. Nevertheless, the offspring of both groups of Tx mothers achieved normal to elevated basal secretion of GH before the end of gestation and continued to have elevated basal secretion of GH through the 30th day of postnatal life as compared with the control progenies.

Discussion

An understanding of the interaction of GH and thyroid hormones (T_4 and T_3) both of maternal origin and fetal-neonatal origin has become critical to our comprehension of brain development and mentation. It has been obvious for many years that hypothyroidism in the developing fetus and in the neonate, if left untreated, results in severe mental retardation. More recently, it has been shown that maternal hypothyroxinemia results in a variety of learning and behavioral deficits (21). Man and Serunian (31) have demonstrated this in the human by a series of studies that culminated in a report of a long-term study of infants born to hypothyroxinemic women.

Some years ago, we developed an animal model to further characterize the hormonal and metabolic defects of the gestationally hypothyroid mother. Some important progress has been made. The dogma that significant amounts of thyroid hormones do not cross the placenta has been shown to be erroneous. We have shown in the rat that there may be a very significant placental transport of thyroid hormones in either direction (21, 23, 24, 28). This has been confirmed in both the rat (26, 27) and the human (25). Because it has been shown that GH itself may also affect brain development and mentation, even by administration to the mother during gestation (16–18), and that maternal, prenatal, and postnatal GH secretion is regulated by thyroid hormones (8–11), it becomes necessary to understand the interaction and control of secretion of GH and thyroid hormones in the progenies of Tx mothers.

In the present study it was of interest that the onset of fetal GH secretion and the eventual basal secretory pattern were very different between the fetuses of the two sets of Tx mothers. GH administration to Tx mothers accelerated by a full day or more the onset of the secretion of GH in their fetuses, and the basal level of GH secretion in these fetuses remained elevated over those of the offspring of untreated Tx mothers through the first day of life. Basal GH secretion in these progenies of GH-treated Tx mothers remained elevated through the time of puberty, i.e., 30 days of age. During the period of 5–30 days of age, this is true also for the progenies of untreated Tx mothers. We have shown previously (23) that the development of the pituitary thyroid-stimulating hormone-thyroid axis is grossly altered also in the progenies of both Tx mothers and GH-treated Tx mothers. The onset of T_4 and T_3 secretion is mildly delayed in these progenies, but they are hyperthyroxinemic by term such that there is a reverse transport of T_4 from fetus to mother (23). During the postnatal period, they develop, by 30 days of age, a significant degree of hypothyroxinemia, and normal serum T_4 and T_3 levels are not obtained until the adult stage and then only with elevated serum thyroid-stimulating hormone levels. Even so, the tissue, brain, and liver levels of T_4 and T_3 are significantly less and rT_3 greater than those of controls in fetuses before the onset of fetal thyroid function (maternal origin), after the onset of thyroid function, and throughout the postnatal period in offspring of Tx and GH-treated Tx mothers (21, 28). Although it is well established that T_3 is a regulator of GH secretion, there is a surprising lack of association between GH secretion and T_4-T_3 secretion in these offspring of Tx and GH-treated Tx mothers. Therefore, reduced basal secretion of GH in the progenies of Tx mothers is not a candidate for the learning and behavioral deficits observed in these offspring (20). However, the delayed onset of GH secretion in these fetuses could result in subtle alterations of brain cell organization and function. Multiple metabolites (amino acids and glucose) and hormones (insulin-like growth factors), as well as T_3, have been shown to be involved in the regulation of GH secretion and, there-

fore, control of fetal and neonatal growth (32, 33). Our animal model differs significantly from those studied previously because in most studies the fetuses as well as the mothers were rendered hypothyroid by either goitrogen administration or by iodine deficiency. We can only speculate that the reason for the elevated basal GH secretion in the progenies of Tx mothers is due to failure of the GH to exert adequately its normal physiological effects necessary to induce normal feedback regulation.

It is most likely that the alteration of maternal-fetal transfer of T_4 and T_3 in mid- to late gestation results in abnormal brain development in the offspring of Tx mothers (28). Mid- to late gestation is the period of neuronal proliferation and migration. The prenatal and postnatal alterations of T_4 and T_3 secretion in the progenies of Tx mothers may also affect normal glia cell development and neuronal myelination (23).

The GH-treatment of the Tx mother results in partial alleviation of some of the developmental and behavioral deficits in their offspring as compared with those of untreated Tx mothers, perhaps as a result of improved placental function in these mothers (16–18). In fact, we have demonstrated previously a partial alleviation of the hypoglycemia and tissue glycogen deficits in the fetuses of Tx mothers by GH administration to these Tx mothers (34–36). Also amino acid transport, amino acid utilization, and total protein content of tissues are to a great extent normalized in the fetuses of GH-treated Tx mothers (21, 22). However, it is confounding that GH treatment of the Tx mother does not prevent the excessive fetal and neonatal mortality rate induced by mild maternal hypothyroidism. Additional studies are in progress concerning tissue levels of hormones at various ages, receptor binding, and the effects on polyribosomal populations and protein synthesis in these progenies of Tx mothers.

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