- Trabajo realizado por el equipo de la Biblioteca Digital de CEU-Universidad San Pablo

- Me comprometo a utilizar esta copia privada sin finalidad lucrativa, para fines de investigación y docencia, de acuerdo con el art. 37 de la M.T.R.L.P.I. (Modificación del Texto Refundido de la Ley de Propiedad Intelectual del 7 julio del 2006)

0013-7227/88/1222-0450$02.00/0
Endocrinology

Vol. 122, No. 2
Printed in U.S.A.

Different Response to Maternal Hypothyroidism during the First and Second Half of Gestation in the Rat*

BARTOLOMÉ BONET AND EMILIO HERRERA

Departamento de Bioquímica, Facultad de Medicina, Universidad de Alcalá de Henares and Hospital Ramón y Cajal, 28034-Madrid, Spain

ABSTRACT. Female rats were mated and thyroidectomized (T) on the same day and divided into four groups. Three groups were subsequently treated daily with 1.8 μg L-T_4/100 g body wt: 1) for the first 12 days [T + T_4 (I)]; 2) from the 12th day until death [T + T_4 (II)]; or 3) for the entire 21-day study [T + T_4 (I + II)]. The other T animals were maintained without treatment (T), and another group of mated rats were sham operated (C). Maternal body weight increase during gestation did not differ between T + T_4 (I + II) and C dams, whereas it was smaller in T dams from the 7th gestational day onward. Neither interruption of T_4 treatment in the T + T_4 (I) rats after the 12th day nor treatment initiated at that time in the T + T_4 (II) group modified their body weights. At day 21, the weights of the maternal conceptus-free body and liver, the placenta, and the fetuses were lower in the T and T + T_4 (II) animals than in either the C and the T + T_4 (I + II) animals. Maternal plasma T_4 and pituitary GH content were reduced, and plasma TSH was enhanced in both T and T + T_4 (I) dams. In fetuses, plasma TSH concentration was augmented in T and T + T_4 (I) rats and unchanged in T + T_4 (II) animals when compared with those of T + T_4 (I + II). Pituitary GH content was reduced in T and T + T_4 (II) fetuses and unchanged in the T + T_4 (I) group. We propose that maternal thyroidectomy greatly decreases the thyroid hormone levels in embryonic structures during the first half of gestation and inhibits normal maternal metabolic changes during this period. In addition to interfering with normal fetal development, these effects reduce the quantity of maternal substrates available to fetuses during the last phase of gestation. In contrast, when maternal hypothyroidism occurs during the second half of gestation, the effects are not as detrimental because fetal thyroid gland activity is adequate, and maternal catabolic adaptations are not impaired. (*Endocrinology* **122:** 450–455, 1988)

THE PATHOGENIC mechanism involved in the development of endemic cretinism is not yet completely understood. Under normal physiological conditions, the variables of thyroid function in the newborn show no correlation with those of the mother, whereas the infants of hypothyroxinemic mothers have an increased risk of lower mental development (1) and, if the hypothyroxinemia is caused by severe iodine deficiency, of being cretins (2), which suggests that maternal thyroid status plays a decisive role. This hypothesis has been substantiated by studies in regions with very severe endemic goiter (3), although other possible effects of goitrogenic substances acting directly on fetal thyroid function and/or placental iodide transport cannot be dismissed. In pregnant rats both iodine deficiency and thyroidectomy have been reported to cause fetal growth retardation (4–7) and permanent postnatal alterations (8), although some studies indicate no changes (9–11). It has recently been shown that both maternal iodine deficiency and maternal thyroidectomy cause a substantial thyroid hormone deficiency in embryonic tissues (4, 5). This condition is most pronounced during the first half of gestation, both before the onset of fetal thyroid function, which occurs some 17–18 days after conception in the rat (12), and before the appearance of thyroid hormone receptors, which occurs after the 12th day of gestation (13). In addition to the possibility that early thyroid hormone deficiency in the fetal tissues may delay fetal development, the maternal hypothyroid condition may also intervene adversely. Metabolic adaptations during gestation involve a substantial increase in maternal carcass fat in the first half of gestation (14), a phase that has been called anabolic (15) and which lasts until the onset of rapid conceptus growth. The present study with T_4 treatment during specific gestational periods of thyroidectomized pregnant rats was performed to determine whether maternal hypothyroidism during only the first 12 days of gestation causes delay in fetal development and alters the normal maternal metabolic adaptations in the gestational state.

Received February 24, 1987.
Address requests for reprints to: Emilio Herrera, Ph.D., Servicio de Bioquimica, Hospital Ramon y Cajal, Ctra. Colmenar km 9, 28034 Madrid, Spain.
* Supported by grants from the Fondo de Investigaciones Sanitarias de la Seguridad Social and from the Comisión Asesora de Investigaciones Cientifica y Tecnica, Ministerio de Educación y Ciencia of Spain.

Materials and Methods

Animals and experimental design

Female virgin Wistar rats from our own colony, weighing 180–200 g, were housed in a temperature-controlled room (22

± 1 C) with 12-h light, 12-h dark cycles, and fed a Purina Chow diet (Panlab, Barcelona, Spain). Animals were mated (day 0 of gestation, as confirmed by the presence of sperm in vaginal smears), and surgically thyroidectomized (T) under ether anesthesia. Care was taken to spare the parathyroids. Another group of pregnant rats was subjected to sham operation and used as intact controls (C). Starting the day after surgery, three groups of rats received a daily ip injection of a solution containing 1.8 μg T_4/100 g body weight for different specified periods: 1) for the first 12 days [T + T_4 (I)]; 2) from the 12th day until death [T + T_4 (II)]; or 3) for the entire 21-day study [T + T_4 (I + II)]. The T_4 dose was chosen on the basis of our previous laboratory experience (16, 17) which showed that it produces a euthyroid metabolic state. A daily ip injection of 0.5 ml 0.9% NaCl was given to all animals not receiving T_4 [the C and T groups during the entire study and both the T + T_4 (I) or T + T_4 (II) group when they were not receiving T_4]. On the 21st day of gestation, at a time corresponding to 22–24 h after the last T_4 or saline injection, the rats were decapitated, and their blood was collected from the neck onto dried, heparinized plates. The two uterine horns were immediately dissected out and weighed with their content to obtain the whole conceptus weight. Fetuses and placenta were excised, and after weighing the fetuses were decapitated for bleeding into heparinized tubes. The plasma of all the fetuses from the same dam was pooled and processed as a single sample. Maternal and fetal pituitaries were removed and homogenized in 1 ml distilled water. The plasma and pituitary homogenates were stored at −80 C until assay.

Processing and analysis of the samples

Pituitary and plasma GH and plasma TSH contents were measured by specific rat RIAs which were kindly provided by the Rat Pituitary Hormone Distribution Program of the NIADDK. Plasma T_4 was determined with the highly sensitive and specific RIA described by Weeke and Orskov (18), as modified for the rat by Obregon *et al.* (19).

Statistical analysis

Mean values ± SEM are given. The significance of difference between means of two groups was obtained with Student's *t* test and for more than two groups with the Newman-Keuls' test (20).

Results

Body weight change during gestation

Increases in body weight during gestation in C and T dams, treated with 1.8 μg T_4/100 g body wt for different periods or untreated, are compared in Fig. 1. These changes were similar in C and T dams receiving T_4 treatment throughout the entire gestational period [T + T_4 (I + II)]. When T_4 treatment was discontinued in T dams from the 12th to the 21st gestational day, normal body weight increase was not modified [T + T_4 (I), Fig. 1]. On the contrary, when T dams received no T_4 treatment (T), their weight gain was greatly diminished and their weight was significantly lower ($P < 0.05$) than those of C and T + T_4 (I + II) dams from the 7th day after thyroidectomy onward (Fig. 1). T_4 treatment of T dams starting on the 12th gestational day [T + T_4 (II)] did not improve their poor body weight increase as compared with T animals (Fig. 1). In all the groups body weight changes from the 12th gestational day were parallel, so that when the weight value at day 12 was considered as 100% for all groups, no significant differences among them were detected up to the 21st day, indicating that from day 12 of gestation the mother's body weight is independent of her thyroid hormone supply. Body weight change during gestation has both maternal and conceptus components. These two were distinguishable in the T animals because whole conceptus weight was estimated in some rats from each group. As shown in Table 1, body weight change through gestation in both the T and T + T_4 (II) dams was significantly lower than in T + T_4 (I + II) rats, whereas no difference was detected between T + T_4 (I) *vs.* T + T_4 (I + II) dams. These intergroup differences were due more to maternal structures than to conceptuses, as both net (conceptus-free) maternal body weight increase and maternal liver weight were lower in T and T + T_4 (II) animals than in T + T_4 (I + II) rats, from which T + T_4 (I) rats did not differ (Table 1). Conceptus weight was similar in all groups, whereas placental and fetal weights in groups T and T + T_4 (II) were lower than in T + T_4 (I + II) (Table 1). Although not systematically measured, the number of live fetuses per dam was lower in T (8.4 ± 0.9, n = 5) than in T + T_4 (I + II) dams (11.1 ± 0.2, n = 5) ($P < 0.05$), which, together with the above mentioned findings, indicates that the amount of amniotic fluid was greater in the former group. No differences were found in any of these variables between T + T_4 (I + II) and C animals (Table 1).

Maternal T_4, TSH, and GH concentrations

As shown in Table 2, values of both plasma T_4 and TSH concentrations and pituitary GH content were similar in T + T_4 (I + II) and C dams, indicating that the former were euthyroid. The T dams showed a greatly reduced plasma T_4 concentration and pituitary GH content, whereas their plasma TSH concentration had risen markedly. While these hormone concentrations were very similar in T and T + T_4 (I) dams, values in T + T_4 (II) were almost normal and did not differ from those of T + T_4 (I + II) rats.

Fetal TSH and GH concentrations

Plasma TSH concentration and pituitary GH content in fetuses from all the groups studied on the 21st day of gestational age are shown in Table 3. It can be seen that, when compared to the T + T_4 (I + II) group, fetuses from T and from T + T_4 (I) dams showed an augmented

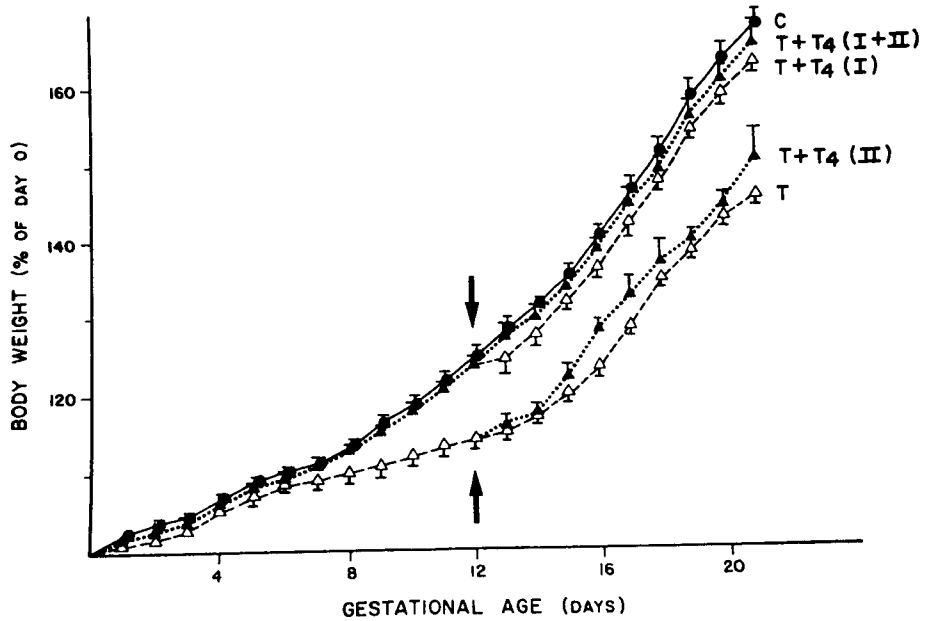

FIG. 1. Percentual body weight changes throughout gestation in T rats treated daily with T_4 (1.8 μg/100 g BW) from day 0 to 12 of gestation [T + T_4 (I)], from day 12 to 21 [T + T_4 (II)], or throughout the gestational period studied [T + T_4 (I+ II)] and in sham-operated controls (C). Differences in the mean weights of the T and T + T_4 (II) and those of C and the T + T_4 (I) group were statistically significant from the 7th day of gestation and thyroidectomy, by the Newman-Keuls test ($P < 0.05$). Absolute body wt values at day 0 of gestation for the groups were: 195 ± 4 for C, 209 ± 5 for T + T_4 (I + II), 201 ± 5 for T + T_4 (I), 189 ± 6 for T + T_4 (II), and 207 ± 6 for T. For simplification, weight recorded during the first 12 days in which two groups received the same treatment were pooled in pairs: T + T_4 (I + II) and T + T_4 (I); and T and T + T_4 (II). In all cases, data corresponding to days under T_4 treatment are shown as *black triangles* (▲·····▲), and data from untreated rats are shown by *open triangles* (Δ– – –Δ), whereas intact controls are shown by *black circles* (●————●).

TABLE 1. The weight of maternal and conceptus structures on the 21st day of gestation in untreated T rats or rats treated with 1.8 μg T_4/100 g body wt for different gestational periods

Group	Body wt change (Δ) through gestation (wt day 21-wt day 0) (g)	Net maternal body wt increase (Δ-conceptus wt)	Maternal liver wt (g)	Conceptus wt (g)	Placental wt (g)	Fetuses wt (g)
C	133.6 ± 5.4	40.7 ± 5.2	9.51 ± 0.53	68.7 ± 6.2	0.52 ± 0.02	5.61 ± 0.09
T + T_4 (I + II)	128.3 ± 5.5	37.9 ± 4.3	8.70 ± 0.47	76.1 ± 4.2	0.47 ± 0.01	5.29 ± 0.10
T	96.8 ± 5.0[a]	21.2 ± 5.5[b]	7.35 ± 0.28[b]	72.7 ± 6.3	0.43 ± 0.01[b]	4.46 ± 0.18[c]
T + T_4 (I)	131.8 ± 5.6	52.4 ± 4.8	9.09 ± 0.52	74.8 ± 6.0	0.51 ± 0.02	5.01 ± 0.13
T + T_4 (II)	104.5 ± 4.5[a]	15.9 ± 2.6[c]	7.10 ± 0.32[b]	75.1 ± 7.9	0.40 ± 0.02[a]	4.89 ± 0.14[b]

Data are mean ± SEM of 6–12 rats per group. T pregnant rats were treated daily with T_4 (1.8 μg/100 g bw) from day 0 to 12 of gestation [T + T_4 (I)], from day 12 to 21 [T + T_4 (II)], or throughout the gestational period studied [T + T_4 (I + II)], or received no T_4. C, Sham-operated controls. Footnote symbols correspond to the statistical significance with respect to data from T + T_4 (I + II) dams.

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$.

plasma concentration of TSH, whereas in those from the T + T_4 (II) dams the values did not differ from those from T + T_4 (I + II) dams. Pituitary GH content was significantly lower in fetuses from both T and T + T_4 (II) dams than in fetuses from T + T_4 (I + II) dams, whereas values in fetuses from T + T_4 (I) dams did not differ from those of the group treated throughout pregnancy. It is interesting to notice that these intergroup differences in fetal pituitary GH content parallel those of fetal body weights (Table 1).

Discussion

In addition to confirming the adverse effects of maternal thyroidectomy on fetal development (5–7), the present findings show three main points which contribute to our understanding of the possible mechanisms involved: 1) the hypothyroid mother has an impaired capacity to build up her own metabolic stores during the anabolic phase of gestation, and this could diminish her ability to fulfill normal fetal metabolic needs during the phase of

TABLE 2. Maternal plasma concentration of T_4 and TSH and pituitary GH content on the 21st day of gestation in untreated T rats or rats treated with 1.8 μg T_4/100 g body wt for different gestational periods

Group	Plasma T_4 (μg/dl)	Plasma TSH (μg/ml)	Pituitary GH (μg/gland)
C	2.32 ± 0.49	0.56 ± 0.06	132 ± 14
T + T_4 (I + II)	1.66 ± 0.19	0.87 ± 0.29	143 ± 16
T	0.05 ± 0.02[a]	5.20 ± 0.80[b]	1.40 ± 0.50[a]
T + T_4 (I)	0.08 ± 0.05[a]	3.56 ± 0.19[a]	6.90 ± 0.80[a]
T + T_4 (II)	1.46 ± 0.29	0.93 ± 0.14	142 ± 42

Data are mean ± SEM of 6–12 rats per group. Experimental conditions are as indicated in Table 1.

[a] $P < 0.001$.

[b] $P < 0.01$.

TABLE 3. Fetal plasma TSH concentration and pituitary GH content on the 21st day of gestation in untreated T rats or rats treated with 1.8 μg T_4/100 g body wt for different gestational periods

Group	Plasma TSH (μg/ml)	Pituitary GH (μg/gland)
C	0.195 ± 0.022	
T + T_4 (I + II)	0.190 ± 0.011	0.810 ± 0.111
T	0.306 ± 0.020[a]	0.248 ± 0.119[b]
T + T_4 (I)	0.335 ± 0.031[b]	0.530 ± 0.101
T + T_4 (II)	0.228 ± 0.030	0.280 ± 0.130[c]

Data are mean ± SEM of 6–12 rats per group. Experimental conditions are as indicated in Table 1.

[a] $P < 0.001$.

[b] $P < 0.01$.

[c] $P < 0.05$.

maximal fetal growth; 2) a reduction in the availability of maternal thyroid hormones for embryonic tissues before fetal thyroid function permanently and negatively affects fetal development, as clearly shown in the reductions of both fetal pituitary GH content and body weight, which were not normalized by maternal treatment with T_4 during the second half of gestation; 3) although the fetus detects and responds to maternal hypothyroidism occurring during the second half of gestation (an increase in fetal plasma TSH concentration was found), the effects of maternal hypothyroidism on late fetal development are negligible, in spite of this being the phase of maximal body weight increase.

Impaired capacity of the hypothyroid mother to fulfill normal metabolic adaptations

In physiological conditions, the pregnant mother builds up metabolic stores during the first half of gestation (14, 21, 22), a period in which fetal development is very slow. The present results show that conceptus-free maternal body weight increase is greatly impaired during this gestational phase in the T pregnant rat, and the impairment is maintained during the second half of gestation. It is well known that thyroid hormones are required for normal anabolic pathways (for a review see Ref. 23). The observed reductions in body and liver weight in the untreated T rats indicate that maternal hypothyroidism during the first half of gestation impairs the anabolic changes that normally occur during this phase, therefore impeding metabolic adaptations during the second half of gestation when the fetal pumping of substrates from the mother is maximal.

Reductions in the availability of maternal thyroid hormones for the embryo during early gestation

Whereas the present experimental design did not allow determination of thyroid hormone concentrations in embryonic tissues, Morreale de Escobar *et al.* (5) have recently reported that maternal thyroidectomy reduces both T_4 and T_3 concentrations in embryotrophoblasts, the effect being heaviest before day 17 of gestation. The present findings on reductions of pituitary GH content in 21-day-old fetuses from both untreated T dams and T dams receiving T_4 treatment from the 12th day of gestation are in agreement with the hypothyroidism evident during the first stage of intrauterine development in embryos of T mothers. The observed restoration of pituitary GH content in fetuses from T dams receiving T_4 treatment only during the first 12 days of gestation indicates that reduced availability of maternal thyroid hormones during the second half of the gestational period may be partially offset by the onset of fetal thyroid function in this phase (12). This compensation is possible under certain conditions, as in this experiment, in which the diet was not iodine deficient and the fetal gland could synthesize sufficient amounts of thyroid hormones. At late gestation, fetuses from T rats have higher than normal T_4 and T_3 concentrations in some tissues such as lung and brain (5) and plasma (7), suggesting a fetal hyperthyroid condition. Our findings of higher plasma TSH levels in fetuses from both untreated T dams and T dams treated with T_4 until day 12 of gestation agrees with this, and may represent a way of supplying the hypothyroid mother with T_4, as suggested by Gray and Galton (24). This compensatory reaction of the fetal thyroid gland to maternal thyroidectomy when there is no iodine deficiency may explain why fetal growth is not as severely inhibited as could be expected. Although most studies, including the present, show a moderate reduction in fetal body weight in T pregnant rats (5–7), others report no change (11), indicating some compensatory action. This compensation may not occur when maternal hypothyroidism is associated with an iodine-deficient diet and/or with the presence of goitrogenic factors, as occurs in certain areas of severe endemic goiter (3, 25, 26). These factors hinder adequate fetal thyroid activity and cause marked thyroid hormone deficiency in embry-

onic tissues throughout intrauterine life, as recently shown in the iodine-deficient pregnant rat (4).

Normal fetal development when the mother becomes hypothyroid during the second half of gestation

Maternal hypothyroidism (documented by reductions in plasma T_4 and pituitary GH content, and an increment in plasma TSH) limited to the second half of gestation was found not to affect conceptus-free maternal body and liver weights, indicating the presence of normal endogenous metabolic stores which adequately fulfill fetal needs. This conclusion is also supported by the normal levels of circulating metabolites (glucose, glycerol, triglycerides, ketone bodies, amino acids) found in these animals at late gestation as well as their normal metabolic response to starvation (our unpublished results), which is, however, decreased in rats that have been hypothyroid since the onset of gestation (27). During the last part of gestation, catabolic manifestations are enhanced in the mother (15, 28, 29) indicating that thyroid deficiency does not impair these metabolic adaptations. This conclusion agrees with previous reports of normal or even enhanced lipolytic activity in the starved T nongravid rat (17, 30), and suggests that whereas the hypothyroid condition greatly impairs anabolic pathways (which play an important role in the first half of gestation), it does not affect the catabolic adaptations required in late gestation.

In summary, the present results show that maternal hypothyroidism produced by thyroidectomy adversely affects fetal development, and this damage is produced during the first stages of embryonic life by affecting both fetal and maternal structures. When maternal hypothyroidism occurs during the second half of gestation, and in spite of this being the period of maximal fetal growth, the effects are not as detrimental because normal maternal catabolic adaptations are not impaired and the fetal requirements for thyroid hormones are met by the activity of the fetus' own thyroid gland. These conclusions are still based on circumstantial evidence, and it is not yet possible to evaluate the relative importance of the different mechanisms that might be involved.

Acknowledgments

The authors thank Dr. Morreale de Escobar for her encouragement and advice in the performance of this study, Dr. Trinidad Jolin for her help in the hormonal determinations, and Ms. Carol F. Warren for her editorial assistance.

References

1. Man EB, Serunian SA 1976 Thyroid function in human pregnancy. IX. Development or retardation of 7-year-old progeny of hypothyroxinemic women. Am J Obstet Gynecol 125:949
2. Pharoah POD, Ellis SM, Williams ES 1976 Maternal thyroid function, iodine deficiency and fetal development. Clin Endocrinol (Oxf.) 5:159
3. Thilly CH, Delange F, Lagasse R, Bourdoux P, Ramioul L, Berquist H, Ermans, AM 1978 Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. J Clin Endocrinol Med 47:354
4. Escobar del Rey F, Pastor R, Mallol J, Morreale de Escobar G 1986 Effects of maternal iodine deficiency on the L-thyroxine and 3, 5, 3′-triiodo-L-thyronine contents of rat embryonic tissue before and after onset of fetal thyroid function. Endocrinology 118:1259
5. Morreale de Escobar G, Pastor R, Obregon MJ, Escobar del Rey F 1985 Effects of maternal hypothyroidism on the weight and thyroid hormone content of rat embryonic tissues, before and after onset of fetal thyroid function. Endocrinology 117:1890
6. Porterfield SP, Hendrich ChE 1975 Effect of maternal hypothyroidism on maternal and fetal tissue glucose-1-^{14}C incorporation in rats. Horm Res 6:236
7. Hendrich CE, Porterfield SP, Galton VA 1979 Pituitary-thyroid function on fetuses of hypothyroid and growth hormone treated hypothyroid rats. Horm Metab Res 11:362
8. Bakke J, Lawrence NL, Robinson S, Bennett J 1975 Endocrine studies of the untreated progeny of thyroidectomized rats. Pediatr Res 9:742
9. Fukuda H, Greer MA 1978 Comparison of pituitary-thyroid maturation in the fetuses of rats fed on iodine-deficient or normal diet. Endocrinology 103:613
10. McIntosh GH, Howard DA, Mano MT, Wellby ML, Hetzel BS 1981 Iodine deficiency and brain development in the rat. Aust J Biol Sci 34:427
11. Baksi SN 1978 Effect of maternal thyroparathyroidectomy during gestation on feto-placental development in rats. Indian J Exp Biol 16:1281
12. Nataf B, Sfez M 1961 Debut du fonctionnement de la thyroide foetal du rat. C R Soc Biol (Paris) 156:1235
13. Perez-Castillo A, Bernal J, Ferreiro B, Pans T 1985 The early ontogenesis of thyroid hormone receptor in the rat fetus. Endocrinology 117:2457
14. Beaton GH, Beare J, Ryu MH, McHenry EW 1954 Protein metabolism in the pregnant rat. J Nutr 54:291
15. Freinkel N 1980 Of pregnancy and progeny. Diabetes 29:1023
16. Llobera M, Seibel MJ, Herrera E 1978 Metabolic response to short periods of starvation in hypo- and hyperthyroid rats. Horm Metab Res 10:319
17. Seibel MJ, Llobera M, Herrera E 1978 Effects of glucose, insulin and adrenalin on glycerol metabolism in adipose tissue hypothyroid rats. Mol Cell Endocrinol 10:307
18. Weeke J, Orskov H 1975 Ultrasensitive radioimmunoassay for direct determination of free triiodothyronine concentration in serum. Scand J Clin Lab Invest 35:237
19. Obregon MJ, Pascual A, Morreale de Escobar G, Escobar del Rey F 1979 Pituitary and plasma thyrotropin, thyroxine and triiodothyronine after hyperthyroidism. Endocrinology 104:1467
20. Snedecor GW 1956 Statistical Methods, ed. 5. Iowa State University Press, Ames, IA
21. Knopp RH, Saudek CD, Arky RA, O'Sullivan JB 1973 Two phases of adipose tissue metabolism in pregnancy: maternal adaptations for fetal growth. Endocrinology 92:984
22. López Luna P, Muñoz T, Herrera E 1986 Body fat in pregnant rats at mid- and late-gestation. Life Sci 39:1389
23. Freinkel N, Metzger BE 1971 Hyperthyroidism: metabolic changes. In: Werner SC, Inbar SH (eds) Thyroid. Harper & Row, New York, p 574
24. Gray B, Galton VA 1974 The transplacental passage of thyroxine and foetal thyroid function in the rat. Acta Endocrinol (Copenh) 75:725
25. Ermans AM, Delange F, Van Der Velden M, Kinthaert J 1972 Possible role of cyanide and thiocyanate in the etiology of endemic cretinism. Adv Exp Med Biol 30:455
26. Stanbury JB, Fierro-Benitez R, Estrella E, Milutinovic PS, Tellez MU, Refetoff S 1969 Endemic goiter with hypothyroidism in three generations. J Clin Endocrinol Metab 29:1596
27. Herrera E, Bonet B, Iglesias R 1980 Metabolic response to star-

vation in the hypothyroid pregnant rat. Biochem Soc Trans 8:538
28. Herrera E, Knopp RH, Freinkel N 1969 Carbohydrate metabolism in pregnancy. VI. Plasma fuels, insulin, liver composition, gluconeogenesis, and nitrogen metabolism during late gestation in the fed and fasted rat. J Clin Invest 48:2260
29. Knopp RH, Herrera E, Freinkel N 1970 Carbohydrate metabolism in pregnancy. VIII. Metabolism of adipose tissue isolated from fed and fasted pregnant rats during late gestation. J Clin Invest 49:1438
30. Montoya E, Herrera E 1974 Effect of thyroid status on glycerol metabolism in adipose tissue of fasted male rats. Horm Res 5:129