Graves' Disease

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Graves' disease is a primary autoimmune disorder characterized by the production of thyroid-stimulating antibodies (TSAb) directed against the receptors for thyroid-stimulating hormone (TSH) on the thyroid cell. TSAb mimics the action of TSH and stimulates excessive production of thyroxine (T_4) and L-tri-iodothyronine (T_3), which in turn results in the clinical picture of hyperthyroidism.

Graves' disease is characterized by lifelong exacerbations and remissions and has a peak incidence in the reproductive years. Many women with Graves' disease or a history of the problem become pregnant. The unique feature of these pregnancies is that they involve two patients, i.e., a mother who can be examined easily, assessed, and treated and a fetus who is difficult to evaluate and at risk in an abnormal intrauterine environment that may adversely affect viability, regulation of cellular development, and quality of life during the entire postnatal life span. Since the metabolic status of the mother may not correlate with that of the fetus, it is important to understand normal maternal-fetal thyroid physiology, the interpretation of thyroid function tests during pregnancy and the fetal risk-benefit ratio of therapeutic measures advised for the mother with Graves' disease.

The diagnosis and management of Graves' disease are more difficult during pregnancy because symptoms of early gestation are similar to those of hyperthyroidism, and tests of thyroid function are modified by hormonal changes which increase thyroxine-binding globulin (TBG). Moreover, the diagnostic and therapeutic use of radioactive materials is contraindicated. This chapter will focus on maternal-fetal thyroid relationships, pathogenesis, diagnosis, differential diagnosis, and management of maternal and/or fetal Graves' disease during pregnancy. The assessment of infants who have had abnormal thyroid function in utero and the possible long-term implications of these problems will also be considered.

Maternal-Fetal Thyroid Relationship During Pregnancy

During pregnancy maternal thyroid function is normal. An increase in the serum concentration of total T_4 occurs early in the first trimester because of an increased binding capacity of TBG secondary to a rise in serum estrogen levels. This metabolic alteration persists until 6-12 weeks postpartum. The normal limits for serum T_4 concentrations are 2-4 μg/dl higher during these periods. Harada et al.[1] have reported a slight but significant rise in absolute free T_4 levels from 11 weeks' gestation onward and an elevation of free tri-iodothyronine (FT_3)

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values at 13–20 weeks. However, the slightly increased levels were not above the range for normal nonpregnant control subjects. Pituitary TSH levels are within normal limits throughout pregnancy, with a slight but significant reduction in serum TSH values (within the normal range) during early gestation (9–12 weeks), when chorionic gonadotropin (hCG) concentrations are highest.[1]

Figure 1 depicts maternal-placental-fetal thyroid relationships from midgestation until term. The cerebral cortex receives external and internal stimuli, which in turn modulate the synthesis of hormones in the brain and hypothalamus. In the rhesus monkey, the administration of thyrotropin-releasing hormone (TRH) to the mother results in placental transfer with fetal stimulation of TSH secretion from a hypersensitive pituitary gland and release of thyroidal T_4 and T_3.[2] The placenta is not permeable to TSH. There is no evidence in humans or experimental animals that maternal TRH influences fetal pituitary-thyroid function.

Three placental thyroid stimulators have been identified. The beta subunit of hCG is structurally homologous with the beta subunit of TSH and has maternal thyrotropic activity. Harada et al.[1] have detected very low levels of chorionic TSH (hCT) in about one-third of maternal sera during pregnancy and concluded that hCT does not influence the control of thyroid function during gestation. Most detectable levels of hCT were at the low portion of the standard curve, where the influence of nonspecific serum factors may be considerable. TRH activity has been detected in extracts of human placenta and shown to originate endogenously within the placenta.[3] Placental TRH has less biologic activity than synthetic TRH and is degraded more slowly by human serum. Although the presence of placental TRH may have potential implications for maternal and/or fetal thyroid regulation, no such correlations have been made to date.

The development of the fetal thyroid gland and an integrated fetal hypothalamic-pituitary-thyroid neuroendocrine control system occur autonomously without apparent maternal influence.[4] There is minimal placental transfer of T_4 and T_3 in humans. In the fetus at 18–20 weeks' gestation there is an increase in pituitary and serum levels of TSH and in thyroid secretory activity of T_4. Fetal T_4 is preferentially monodeiodinated to reverse T_3 (rT_3), a less active hormone

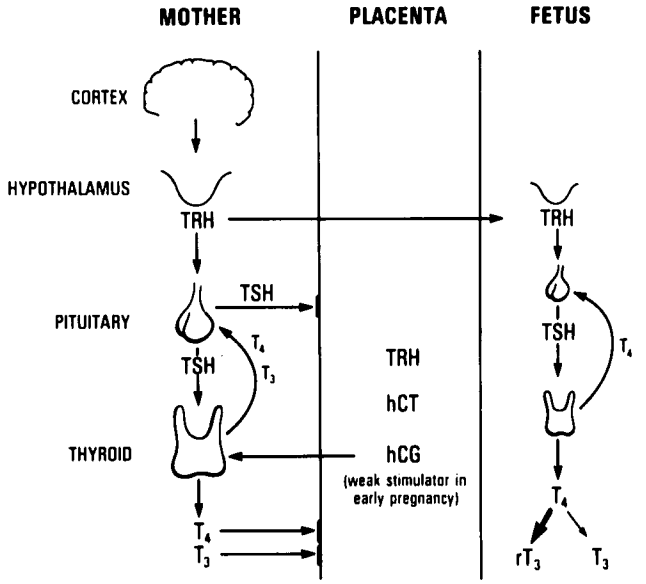

FIG. 1. *Maternal, placental, and fetal thyroid relationships during pregnancy. In the first trimester placental hCG is a weak stimulator of the maternal thyroid. Maternal TRH crosses the placenta, but TSH does not. Placental transfer of T_4, T_3 is minimal. Fetal thyroid function is autonomous.*

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than T_3. The maturation of fetal thyroid function is mediated by hypothalamic stimulation of pituitary TSH and iodothyronine feedback control.[4]

Pathogenesis of Maternal and Fetal Graves' Disease

The full details of the pathogenesis of Graves' disease are unclear, and the cause of the disease is unknown. Early descriptions of the disorder invoked emotional, hereditary, infectious, or sympathetic nervous system abnormalities as important etiologic factors. In 1956 Adams and Purves[5] described an abnormal long-acting thyroid stimulator (LATS) in the blood of some patients with Graves' disease. This landmark observation was demonstrated by a bioassay in the guinea pig in which the injection of serum from a patient with Graves' disease evoked a prolonged stimulatory effect on the thyroid. Further work demonstrated that LATS was an antibody to a thyroid antigen and present in an immunoglobulin of the IgG class. The development of the concept of the role of humoral immunity in the pathogenesis of Graves' disease has been reviewed by McKenzie et al.[6]

During the 1970s a number of assays were developed to detect the presence of thyroid stimulatory immunoglobulins. Positive assays depended upon stimulation of adenylcyclase from human thyroid tissue slices or membranes (assay method terminology: HTS, human thyroid stimulator; H-TACS, human thyroid adenylcyclase stimulator; TSAb, thyroid-stimulating antibody); binding to human thyroid, preventing, i.e., "protecting" subsequent binding of LATS (LATS-P, long-acting thyroid stimulator protector); or competition with TSH in a TSH receptor assay using human thyroid membranes (TSI, thyroid-stimulating immunoglobulins).

The profusion of methods, differences in methods, and lack of international reference values has impeded clinical observations in patients with autoimmune thyroid disorders. This is a special problem in the management of pregnant women with Graves' disease, because it is generally not possible to have quantitative data concerning the titer of human TSAb during gestation.

The work from many laboratories indicates that TSAb is the stimulatory antibody associated with the hyperthyroidism of Graves' disease. Whether this is the "cause" of the disorder or an "immunologic marker" in genetically suceptible individuals who develop Graves' disease is not yet apparent.

The Graves' triad of goiter, exophthalmos, and hyperthyroidism has a strong predilection for women (7 to 1). The onset is often precipitated by emotional trauma, or periods of metabolic stress such as puberty, pregnancy, or the menopause. Some investigators have suggested an autosomal recessive pattern of inheritance,[7] but others have noted a remarkable parent-to-child transmission over several generations which indicated a possible dominant inheritance.[8,9]

The time of onset and degree of expression vary greatly in Graves' disease, and there are also associated pleiotropic findings. Population studies have shown an increased frequency of haplotypes HLA-B8 (DW3) in Caucasian, HLA-BW46 in Chinese, and HLA-BW35 in Japanese patients. In the pathogenesis of Graves' disease the HLA associations do not indicate how the genes produce their effect, and it is likely that at least one gene is related to immune responsiveness.[10]

In pregnancies complicated by Graves' disease, TSAb's readily cross the placenta to stimulate the fetal thyroid. This can result in fetal hyperthyroidism if the TSAb titer is sufficiently high.

It is difficult to compare TSAb data in infants reported to have neonatal Graves' disease, because such pregnancies are uncommon; different tests have been used to evaluate stimulatory immunoglobulins or their effects, and rarely is information available on serum from the mother, cord, newborn (days 1-3), and young infant (2 weeks to 6 months). Moreover, family pedigree studies and identification of HLA

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haplotypes that carry Graves' disease susceptibility (B8, DR3-positive) are unavailable in reported cases of affected and nonaffected infants at risk for Graves' disease and their families. Thus, immunogenetic correlations have not been possible in these pregnancies. At present, measurement of TSAb obtained by stimulation of the adenyl-cyclase-cAMP system in human thyroid plasma membranes appears to be a specific and sensitive marker for Graves' disease. This procedure has a high degree of specificity and sensitivity but requires relatively normal tissue obtained at thyroid surgery. The test is not available in commercial laboratories.

Despite the methodologic problems, several clinical observations have been noted during pregnancy 1) high maternal titers of TSAb are more likely to be associated with neonatal Graves' disease than low titers[11]; 2) LATS (detected in a mouse bioassay) titers may be negative in mothers with positive TSAb assays (thyroid slice, adenyl-cyclase-cAMP assay); 3) newborn infants with Graves' disease may have persistent hyperthyroidism for years and long after the biologic half-life of transplacental passage of TSAb; 4) three infants with congenital neonatal Graves' disease have been born to mothers with no history of a thyroid disorder; and 5) delayed-onset (aged 2-4 months) neonatal Graves' disease has been reported in two infants of a mother with Hashimoto's disease who was negative for LATS and LATS-P but whose serum had a TSAb inhibitor.

The clinical spectrum of Graves' disease in utero is quite broad, just as it is during other periods of life. Fetal loss is common, and some infants are stillborn or premature. A few affected newborns show widespread evidence of autoimmune disease with generalized hypertrophy of lymphatic tissue and thrombocytopenic purpura. In others, the disease is apparent at birth with goiter or exophthalmos, or both, which may be accompanied by signs and symptoms of hypermetabolism.

In most instances, infants with neonatal hyperthyroidism have a transient disorder lasting 1-5 months.[12] The half-life of thyroid-stimulatory immunoglobulins has been estimated to range from 5 to 14 days. Eleven children have been described with persistent hyperthyroidism that lasted long after the disappearance of transplacental transfer of TSAb. In the studies of Wilroy and Etteldorf[12] and Hollingsworth et al.,[13] persistent neonatal hyperthyroidism lasting many years was associated with a strong family history of Graves' disease and other thyroid disorders.

Zakarija et al. (unpublished observations, 1981, 1982) have made the interesting observation that delayed onset of neonatal Graves' disease may be due to interactions between TSAb and a thyroid-directed inhibitor. In their case report, a mother with Hashimoto's thyroiditis and a family history of Graves' disease was negative for LATS and LATS-P. A unique feature of the LATS-P assay was that progressive dilution (up to 1:200) of the serum uncovered greater activity; i.e., presumably an inhibitor was diluted out. In the TSAb human thyroid slice assay the IgG had a biphasic effect on cAMP production. The dose-response relationship was such that an initial linear increase "plateaued" and then returned to basal values with increasing concentrations of IgG in the assay, implying again the existence of an inhibitor. The first infant born to this mother was found to have Graves' disease at age 4 months. The exact age of onset in unclear. At 4 months TSAb was strongly positive and just measurable at 6 months.

The second child was followed closely from birth, and assay data on serial blood samples indicated the persistence of an inhibitor of TSAb until 45 days of age, when the child became thyrotoxic. Since dilution of the mother's serum increased LATS-P activity and low concentrations of her IgG were more potent than high concentrations in the TSAb assay, the data were compatible with the concept that TSAb and an inhibitor were cleared from the blood of each infant until the TSAb effect became dominant.

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The neonatal period is usually defined as the 1st month after birth, but it is becoming increasingly apparent that in susceptible individuals the immunogenetic predisposition for Graves' disease may be triggered by transplacental passage of TSAb in utero, may be modified by blocking protective antibodies, or may emerge at any period after birth from age 1 day to old age. To date, there has been no documentation of an infant with neonatal Graves' disease with TSAb present but absent in the mother. Individual patients vary in both the time of onset and the expression of the disease. Both may be influenced by environmental, emotional, or perhaps even viral or bacterial infections such as that of *Yersinia enterocolitica,* type 3. No unifying hypothesis for the pathogenesis of neonatal Graves' disease has evolved because a definitive genetic marker has not been identified in affected individuals or those at risk for the disorder.

Diagnosis of Maternal and Fetal Graves' Disease During Pregnancy

Maternal hyperthyroidism, particularly in the early stages, is difficult to diagnose during pregnancy. Many pregnant women experience emotional lability, modest intolerance to heat, nervousness, irritability, and increased perspiration. Appetite and weight gain are variable, and weight loss is not unusual during the first trimester. When these symptoms are associated with a palpable thyroid gland, tachycardia, a slight increase in systolic blood pressure, and borderline elevations of serum T_3 and T_4 values, the possibility of hyperthyroidism may be a concern.

Graves' disease is more common in women with a positive family history of thyroid disease. A careful history and physical examination are the most useful part of the initial evaluation. Pregnant women who are nervous are more likely to have a pulse rate under 100, a pulse pressure < 50 mmHg, cool hands without a fine tremor, normal reflexes, a nonpalpable or barely palpable thyroid gland without a thrill or bruit, and no stare or exophthalmos.

In pregnant women with hyperthyroidism, thyroid function studies are abnormal, with an elevation of serum levels of T_4 and T_3 beyond the expected higher values in normal pregnancy. The resin triiodothyronine uptake test (RT_3U) is in the high normal or elevated range. The free thyroxine index (FT_4I), a calculation used to correct the estimated total T_4 for the amount of TBG present, is increased, as are serum concentrations of free T_3 (FT_3) and free T_4 (FT_4).

Diagnostic studies with ^{131}I are contraindicated, because the radioactive material crosses the placenta and is concentrated in the fetal thyroid gland after 10 weeks' gestation. Table 1 compares thyroid function tests in pregnant and nonpregnant women. Tests for TSAb, when available, are useful when one wishes to determine whether the fetus is at risk for Graves' disease in utero. Higher TSAb titers may be found early in gestation, rather than during late third trimester, because of the immune suppressive effect of pregnancy.

The causes of maternal hyperthyroidism during pregnancy are Graves' disease, the hypermetabolic phase of Hashimoto's chronic thyroiditis, acute (subacute) thyroiditis, toxic nodular goiters, or hydatidiform moles or choriocarcinomas. Table 2 depicts the direction of thyroid function tests and characteristics of the thyroid gland in the differential diagnosis between Graves' disease and other conditions that may be confusing during pregnancy.

Acute (subacute) thyroiditis with *transient* hyperthyroidism is the most common thyroid disorder encountered during pregnancy in both adolescent and older women. These patients often have a tender goiter and hypermetabolic signs and symptoms. A previous history of viral illness is common. Figure 2 is a picture of a young woman who presented at 29 weeks' gestation with an enlarged, tender thyroid gland and signs and symptoms of hyperthyroidism. Tests of thyroid function revealed a serum T_4 of 15.4

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TABLE 1. Thyroid Function Tests in Pregnancy*

Test (Serum)	Method	Normal	Pregnancy	Comment
TSH (μU/ml)	RIA	< 10	No changes	↑ in primary hypothyroidism
T_4 (μg/dl)	RIA	4.5–12.5	↑2–4 μg/dl	↑ normal range secondary to ↑ TBG levels
T_3 (ng/dl)	RIA	90–190	↑25–50 ng/dl	↑ normal range with ↑ TBG levels
R. T_3U (%)	Resin uptake T_3	25–35	↓ to 20–25%	Indirect test of protein binding (not a measurement of T_3)
FT_4 (ng/dl)	Equilibrium dialysis	1.4 ± 0.16	No change	Helpful in evaluating thyroid function in women who are pregnant or on oral contraceptives
Free T_4 or free T_3 index—calculation based on the product of the in vitro resin uptake value of T_3 or T_4 and the serum total T_4 concentration				
Thyroid autoantibodies Thyroglobulin	Hemagglutination	None	May be positive in subacute and Hashimoto thyroiditis and Graves' disease	
Microsomal (MSA)	Hemagglutination	None	May be positive in subacute and Hashimoto thyroiditis and Graves' disease	
^{131}I (%)	Uptake of ^{131}I by thyroid gland	10–25 at 24 hours	**Contraindicated in pregnancy**	
Thyroid stimulating antibodies†	LATS bioassay	Absent	Present in 50% or less patients with Graves' disease	

*Normal values must be determined for each laboratory in which the test is performed.

†Tests for thyroid-stimulating IgG by measurement of adenyl cyclase from human tissue slices or TSH receptor assays are not available in commercial laboratories.

μg/dl and an FT_4I of 17.1. Although the patient was mildly hyperthyroid, fetal heart rate and growth were normal. In order to avoid unnecessary exposure of the fetus to thyroid-blocking agents, we gave the patient no treatment. The patient became euthyroid by 31 weeks' gestation (T_4, 12.7 μg/dl; FT_4I, 9.6) and delivered a normal male infant at term.

In some pregnant patients it is difficult to distinguish between Hashimoto's disease during a hyperthyroid phase and Graves'

TABLE 2. Differential Diagnosis of Graves' Disease During Pregnancy

Diagnosis	Thyroid Tests				Goiter
	T_4, T_3	*FTI*	*FT_4, FT_3*	*TSAb*	
Graves' disease	↑	↑	↑	+	+ Homogeneous, thrill and bruit common
Acute (subacute) thyroiditis	↑ (Transient)	↑ (Transient)	↑ (Transient)	—	+ Frequently tender
Hashimoto's disease	N ↑ or ↓	N ↑ or ↓	N ↑ or ↓	—	+ Firm, may be tender
Anxiety and thyroid enlargement	N	N	N	—	+ Soft, nontender, usually < 8.0 cm

N, normal.

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FIG. 2. *A 17-year-old hyperthyroid woman with acute (subacute) thyroiditis at 29 weeks' gestation. The thyroid was enlarged and tender on palpation.*

disease. In some individuals these two autoimmune disorders coexist ("Hashitoxicosis"). Patients with Hashimoto's thyroiditis often have large, firm, and occasionally tender goiters but no ophthalmologic signs. When serum T_4 levels are > 20 μg/dl, FT_4I, FT_3, and FT_4 are elevated, small doses of propylthiouracil (PTU) (25-50 mg every 8 hours) may be indicated. Treatment, however, may not be necessary if the patient is only mildly symptomatic and maternal weight gain, measurements of uterine height, and fetal heart rate and fetal growth measured by ultrasonography are normal. The fetal evaluation should include serial ultrasonographic examinations for detection of possible intrauterine growth retardation and auscultation of the fetal heart for tachycardia (> 160/min) or bradycardia (< 120/min).

Management of Graves' Disease During Pregnancy

Medical Treatment

Pregnant women with Graves' disease and hyperthyroidism require medication for control of their disease. Figure 3 shows maternal-fetal thyroid relationships during the last half of pregnancy and the placental transfer of possible drugs that may have been administered to the mother.

The therapeutic goal is to achieve euthyroidism or slight hyperthyroidism in the mother and to prevent fetal hypo- or hyperthyroidism. Since PTU crosses the placenta more slowly than methimazole (Tapazole) and blocks not only intrathyroidal synthesis of thyroxine but also conversion of T_4 to T_3 in peripheral tissues, it has become the drug of choice during pregnancy. In most women the disease is gradually brought under control in 3-4

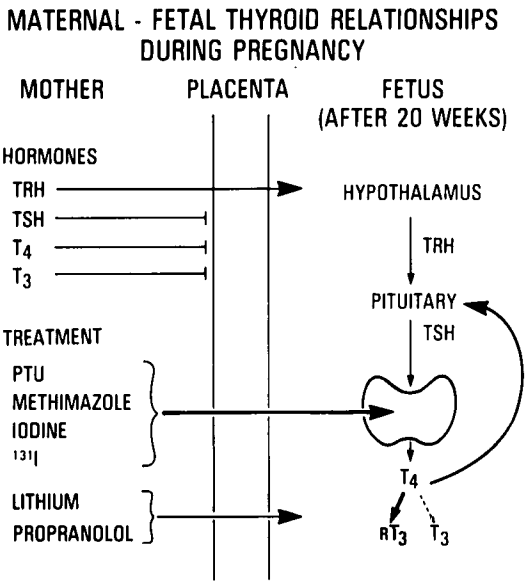

FIG. 3. *Maternal-fetal thyroid relationships and the placental transfer of medications to the fetus.*

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weeks with a dose of PTU of 100 mg or less every 8 hours. During this period careful physical examination of the patient to detect a decrease in pulse (including sleeping pulse rates obtained by the husband), pulse pressure, hyperactivity, tremor, appetite, and emotional lability will indicate improvement. When the serum level of T_4 begins to decrease, the dose can be reduced gradually to 25-50 mg every 6-8 hours. During the late third trimester it may be possible to stop the medication entirely or decrease it to a very small amount (25-50 mg/day). The lower dose or discontinuation of antithyroid medication is usually possible because of a gradual remission during therapy and suppression of immunologic activity during pregnancy.[14]

Maternal Complications of PTU Therapy

In nonpregnant women a generalized erythematous drug eruption is sometimes observed within days to weeks after starting the medication. The rash may be accompanied by fever, sore throat, and arthralgias that are similar to a lupuslike syndrome. The most serious and potentially life-threatening complication is the sudden development of agranulocytosis after 1-2 months of PTU therapy. A baseline complete blood count should be obtained before the medication is started. A follow-up blood count is usually obtained after 1-2 months of medication. More frequent observations are not usually requested, because this complication tends to occur suddenly and without warning in 1 in 300 of the patients who receive PTU. Each patient should be instructed at the onset of drug therapy to stop the medication if any side effects occur and return as soon as possible for reexamination and reevaluation. In some women methimazole can be substituted and is tolerated without problems.

Interestingly, we have not encountered hypersensitivity or idiosyncratic reactions to PTU or methimazole in pregnant women. If such a reaction did occur, propranolol would be the treatment of choice. In some women surgery might be advised with preoperative preparation with propranolol and saturated solution of potassium iodide (SSKI). In severe drug reactions or agranulocytosis, propranolol, iodides, and cortisone might be necessary.

PTU and the Fetus

Although PTU is the major drug used to treat Graves' disease during gestation, the risk-benefit ratio to the fetus must be weighed carefully. The drug may cause both goiter and in utero and neonatal hypothyroidism. In a prospective study of infants at age 1 and 3 days born to hyperthyroid mothers who had been treated with low doses of PTU (100-200 mg/day), Cheron et al.[15] were able to document biochemical evidence of mild transient hypothyroidism even though the infants were clinically euthyroid. The addition of thyroid hormone to maternal PTU treatment has no benefit for mother or infant. Administration of exogenous thyroid hormones is not indicated, because little or no T_4 and T_3 crosses the placenta to "protect" the fetus. In addition, this therapeutic approach increases the likelihood that the infant will receive an excessive exposure to PTU, because the physician may give the mother higher doses of antithyroid drugs to keep her euthyroid.

Burrow[16] has reported the neonatal outcome of 41 pregnancies in 30 patients who received antithyroid medication from 1950 to 1964. In half the cases iodides were administered in addition to PTU. Fetal loss was 12.2%, with 3 spontaneous abortions (2 in mothers who were hypothyroid and on antithyroid medication), 1 ectopic pregnancy, and 1 stillborn. Data were available in 37 infants. Of this group, 5 (13.5%) had goiter unrelated to dose of PTU or time of administration during gestation. All but one of the infants with goiter had also been exposed to iodides. Three of the 5 infants had low butanol-extractable iodine (BEI) levels at age 3-5 days. Protein-bound iodine (PBI) or BEI measurements were available in only 24 of the 37 infants in the 1st week of

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life, and 4 (17%) were in the hypothyroid range. One infant with goiter was mentally retarded, and one hypothyroid infant without goiter was in a mental institution. One set of fraternal twins was of interest. The female was noted to be hyperthyroid at age 2 years and required treatment for 7 years. Her brother had gait difficulty and cryptorchidism. Three additional children whose mothers were treated only with iodides had large congenital goiters.

In a later follow-up of 8 boys and 7 girls from the previous report who had been exposed to PTU in utero and 18 of their siblings, Burrow et al.[17] conducted additional examinations. Psychological testing was carried out in 18 children born to PTU-treated mothers from the original 41 pregnancies, and 17 control siblings. The groups did not correspond exactly to those undergoing medical evaluation. Three of the 15 children in the PTU group were not evaluated medically. The battery of tests was adapted to the age of the patients (PTU exposed: age range 1 year 10 months to 8 years 5 months; control group: age range 2 years to 10 years 6 months). There was no difference for mean group IQ tests, but the standard deviations were large in both PTU-exposed children and their siblings. Height for age and weight for age were both lower in PTU-exposed children.

In 1978 Burrow et al.[18] reported a third follow-up in 28 of the children exposed to PTU in utero and 32 of their siblings (6 children did not have tests on control siblings). Twenty-three of 28 children had been exposed to PTU in the third trimester, one child in the second trimester, and 3 during the first trimester only. Four children were exposed to 400 mg of PTU or more, and 11 children were exposed to 300 mg or more at some time during gestation. Although the median IQ for the total group of children was 100, the range was quite broad (50–132 in the experimental group and 53–122 in the control groups). No information was given on the number of retarded children (IQ 53–80) in each group. Two infants with neonatal thyrotoxicosis were said to have a significant depression of IQ. It was of interest that 5 control siblings of 1 subject with toxic goiter had IQs of 61, 66, 74, 81, and 81. Eleven children who had been exposed in utero to 300 mg PTU or more had a mean IQ of only 85 ± 8SD, 5 children having IQs less than 80. Although Burrow[19] recommends that PTU can be used in the treatment of thyrotoxicosis without major concern that subsequent intellectual development will be affected significantly, the IQ and growth data in 28 of their original 37 children are not very reassuring. Interpretation of the data is further complicated by the fact that half the mothers received iodides during pregnancy and some children received PTU or thyroxine for variable periods after birth.

It is recommended that the smallest possible therapeutic doses of PTU be given to pregnant women with Graves' disease and that no treatment be given for the transient hyperthyroidism of acute (subacute) thyroiditis.

Treatment With ^{131}I

Because of the hazards of in utero radiation exposure to the fetal thyroid gland, radioactive iodine therapy is never knowingly given to pregnant women. Fetal uptake of iodine occurs by 10–12 weeks of gestation. Destruction of the fetal thyroid gland is possible and results in iatrogenic hypothyroidism in utero. Pregnancy tests should be obtained in all women of childbearing age before administration of diagnostic or therapeutic doses of ^{131}I.

Women who have received ^{131}I inadvertently during pregnancy present a difficult problem for the obstetrician and endocrinologist. Since the fetal thyroid has been reported not to trap iodine until 10–12 weeks' gestation, radiation exposure during the first trimester has been felt to be innocuous. Stoffer and Hamburger[20] conducted a survey of 963 physicians to determine the outcome of pregnancy after inadvertent ^{131}I therapy in the first trimester. They reported 237 cases from 116 of 517 physicians who responded. Therapeutic abortion had been advised by 22 physicians for 55 patients. In

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the remaining 182 pregnancies the complication rate (two spontaneous abortions, two stillborn infants, one neonate with biliary atresia, and one with respiratory distress syndrome) was not greater than might be expected. However, six infants were hypothyroid (transient for one), four children had definite mental deficiency, and a fifth had possible minimal mental retardation. The weeks of gestation when ^{131}I was administered were 6 (precise timing uncertain), 9, 12, 14, 15, and 26. None of the mothers had a pregnancy test before the treatment. Thus, three patients who received ^{131}I in the first trimester have been documented to have hypothyroid infants. Follow-up of these children is poor, and expensive psychologic and psychometric testing is rarely done. Thus, there is a tendency to underestimate the number of minimally or moderately impaired children.

The fetal thyroid after 10-12 weeks' gestation has an affinity for iodine 20-50 times that of the maternal thyroid.[19] Maternal irradiation during diagnostic studies has not been reported to have adverse effects upon the fetus.

Maternal treatment with therapeutic doses of ^{131}I after the first trimester results in a risk of in utero fetal hypothyroidism. Maternal counseling is difficult, because the correlation of fetal thyroid function in utero and amniotic fluid concentrations of T_4, reverse T_3 (rT_3), or TSH has not been reliable.[21] Some women elect to have a therapeutic abortion. Others decide to continue the pregnancy, assess fetal thyroid status at birth (cord serum T_4, TSH, fetal thyroid scan with 99mTc pertechmetate), and start thyroid replacement therapy promptly in the infant. Although the early reports of infant development (to age 12 months) were encouraging, a subsequent evaluation has shown that in utero hypothyroidism may not be completely reversible in all children.[22] Two attempts at in utero fetal treatment with thyroxine via the amniotic fluid[23] or by intramuscular injections into the fetus[24] have been difficult and unsuccessful because of the problem of accurate dosage and the need for frequent treatments.

Burrow[19] suggests that when radiation exposure is discovered within a week, maternal treatment with PTU, 300 mg daily, might block the recycling of ^{131}I in the fetal thyroid, because 90% of the dose of ^{131}I is delivered in 10 days.

The possible carcinogenic risk for children who have been irradiated with ^{131}I in utero is unknown. Other forms of radiation exposure of pregnant women have been associated with leukemia in their children many years after birth.[25]

Drugs, such as iodides or propranolol, for the treatment of maternal hyperthyroidism during pregnancy are contraindicated or employed only for brief periods in exceptional circumstances such as hypersensitivity to PTU or methimazole or thyroid storm.

Administration of nonradioactive iodides to pregnant women can result in large fetal goiters, tracheal obstruction, congenital hypothyroidism, and fetal demise. The most common maternal iodide exposure results from oral ingestion of Lugol's iodine solution, SSKI, vaginal suppositories containing betadyne, and the x-ray procedure amniofetography. The administration of conventional doses of iodide—bronchodilator products—to pregnant asthmatic women has been associated with neonatal death from congenital goiter which produced tracheal obstruction. Iodides and PTU are also contraindicated during lactation. Treatment of infants with iodides or iodine antiseptic agents should be avoided in the neonatal period. Premature newborns are at greater risk for iodide-induced-iatrogenic-neonatal hypothyroidism than infants of full-term gestations.

The use of beta blockers such as propranolol during pregnancy is controversial. Propranolol readily crosses the placenta and is excreted in significant quantities in breast milk. Reports of retrospective studies of complicated pregnancies and isolated case reports indicate that this drug may be associated with placental insufficiency, intrauter-

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ine growth retardation, and suppression of the fetal tachycardia response to hypoxia. In newborn infants of mothers who received propranolol, respiratory depression, bradycardia, floppiness, hypoglycemia, and hyperbilirubinemia have been described.

It has been difficult to assess the possible relationship of propranolol to intrauterine growth retardation, because the maternal problems for which the drug is most often given (hypertension or Graves' disease) are also associated with impaired growth in utero. Since maternal hyperthyroidism can usually be controlled relatively easily during pregnancy with reasonable doses of PTU, we have not used beta blockers except in unusual circumstances—e.g., hypersensitivity to PTU or methimazole—because of possible adverse effects on the fetus and neonate.

Surgical Treatment

Subtotal thyroidectomy during the second trimester is an alternative therapeutic approach to Graves' disease during pregnancy. There are no prospective studies that compare the merits of surgical versus medical therapy.

In patients who are advised, or elect, to have surgery during gestation, a preliminary period of 3–4 weeks of PTU is necessary for achievement of a euthyroid state and avoidance of thyroid storm. The usual indications for surgery are failure to control hyperthyroidism by medical means or hypersensitivity to thyroid-blocking agents. Since most spontaneous abortions caused by hyperthyroidism occur during the first trimester and premature labor is a risk in the third trimester, subtotal thyroidectomy is customarily advised during the second trimester. Some surgeons have questioned whether preoperative treatment with Lugol's iodine solution or SSKI is necessary. The use of iodides or propranolol before surgery should be reserved for women who have had hypersensitivity reactions to PTU.

The disadvantage of subtotal thyroidectomy is the risk of postoperative hypoparathyroidism, recurrent laryngeal nerve paralysis, or anesthetic mishap. Worley and Crosby[26] have reported a better maternal and immediate neonatal outcome in 10 pregnant women treated by medical means than in 7 women who had a subtotal thyroidectomy at 8–25 weeks of gestation. Two of the latter patients developed hypoparathyroidism and had stillborn infants. One woman remained thyrotoxic. Four infants did well and one was stillborn, in a pregnancy complicated by preeclampsia and placental abruption. In the group of 10 women who received medical treatment, there was 1 maternal and infant death following thyroid crisis, 1 fetal loss at 18 weeks, 1 infant with neonatal Graves' disease, and 7 living infants. In this small group of patients with a high rate of complications for both mothers and infants and no infant follow-up beyond the immediate delivery period, neither treatment emerged as clearly superior.

In the Mayo Clinic experience from 1946 to 1973 Emslander et al.[27] reported that of 25 surgically treated patients, 22 delivered healthy, viable babies. None of the newborns had goiter or subsequent thyroid problems; and all developed normally, both physically and mentally. One woman had an elective abortion 6 weeks after thyroidectomy, and 2 hypothyroid patients had spontaneous abortions at 14 weeks' gestation. There were no surgical complications.

The assessment of the comparative efficacy of second trimester subtotal thyroidectomy versus medical treatment with antithyroid drugs in decreasing the transplacental passage of TSAb will require careful observations on the outcome of infants at risk. In addition, serial longitudinal observations will be necessary for both mothers and children. Several other factors should be considered: 1) Maternal Graves' disease that is overtreated or undertreated with antithyroid drugs can be associated with fetal loss or an increase in neonatal morbidity and mortality. 2) There are no reports of the surgical management of these pregnancies since the mid-1970s, when the specialities of antenatal endocrinology, perinatology, and neonatology were developed. 3) The known

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cases of mental retardation, goiter, and congenital hypothyroidism (transient or lasting) reported following maternal treatment with antithyroid drugs are difficult to unravel, because they may have been associated with either hyper- or hypothyroidism in utero or the administration of multiple drugs in variable doses and at different times to mothers and newborn infants. Because screening programs are now detecting congenital hypothyroidism in children whose mothers have received antithyroid drugs, it is clear that the prevalence of in utero hypothyroidism is probably higher than previously thought.

It is recommended that women with Graves' disease or a history of the disorder be followed every 2-4 weeks throughout pregnancy. If maternal weight gain, fetal growth, and fetal heart rate (FHR) are normal and maternal levels of serum FT_4 and FT_4I are at high normal or slightly elevated levels on a dose of PTU of 200-300 mg/day, medical therapy is usually continued.[28]

Maternal subtotal thyroidectomy during the second trimester and postoperative replacement therapy with T_4 may be selected as the primary treatment for some women or reserved for others who do not respond to recommended doses of antithyroid drugs or in whom hypersensitivity reactions to PTU develop. Insufficient data are available to assess the relative efficacy and fetal risk-benefit ratio of medical versus surgical treatment. Table 3 outlines a management plan for pregnancies complicated by Graves' disease or a previous history of the disorder. Figure 4 is a convenient longitudinal flow sheet for the maternal-fetal assessment of pregnancies complicated by Graves' disease or other maternal or fetal thyroid disorders.

Assessment of Fetal Thyroid Function In Utero

Both untreated fetal Graves' disease in utero and variable doses of PTU or iodides, or both, can be associated with decreased intellectual performance in children. Thus, it is apparent that better methods are needed for the evaluation of fetal thyroid function in utero.

It is not practical or safe to determine fetal serum levels of T_4, TSH, and reverse T_3 during gestation. Although it is possible to measure thyroid hormone levels in amniotic fluid (AF) throughout pregnancy, it has been disappointing that neither congenital hypo- nor hyperthyroidism has been detected in the human fetus by this means.

Several biophysical methods of fetal assessment may yield helpful information concerning the metabolic status of the fetus. The thyrotoxic fetus may have intrauterine growth retardation, and this can be documented by careful measurement of the uterine fundus at each clinical visit and by serial fetal measurements obtained on ultrasonographic examination.

TABLE 3. Treatment of Graves' Disease During Pregnancy*

First Trimester	Second Trimester	Third Trimester	
Metabolic status	Hyperthyroid patients PTU 50-100 mg/8 hrs	Medical Rx	Postsurgical Rx
1. Euthyroid, no Rx 2. Hypothyroid Synthyroid 0.15 mg/day 3. Hyperthyroid PTU 50-100 mg/8hrs	Monitor FHR† and intrauterine growth Subtotal thyroidectomy 0.15 mg Synthroid daily	0-50 mg PTU daily	0.15 mg Synthroid daily
		Monitor fetus	
		FHR < 130 ↓ PTU > 160 ↑ PTU	FHR > 160 PTU 50-200 mg/day

*Propranolol and iodine solutions are not indicated except in unusual circumstances (hypersensitivity to antithyroid drugs) because of possible adverse effects upon the fetus.

†Fetal heart rate.

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LONGITUDINAL FLOW SHEET FOR PREGNANT WOMEN WITH THYROID DISORDERS

MATERNAL HISTORY

A. DIAGNOSIS:
B. AGE AT ONSET:
C. FAMILY HISTORY:
(Plot kindred on reverse side)
D. TREATMENT:

NAME _____
BIRTHDATE _____
HOSPITAL _____

E. THYROID STATUS AT CONCEPTION:
F. MEDICATION AT CONCEPTION:

TIME		MATERNAL TESTS DURING PREGNANCY												MEDICATION
DATE:	WEEK GEST.	T_4 μg/dl	FT_4I	F T_4 μg/dl	T_3 ng/dl	RT_3U %	TSH μU/ml	Thyroid ab titers Tg	msa	TSAb units	Amnio-centesis	Ultra-sound	NST* CST	

DELIVERY											rT3	INFANT
MATERNAL SERUM												NAME _____
CORD SERUM												BIRTHDATE _____
AMNIOTIC FLUID												HOSPITAL # _____

POST PARTUM										BONE AGE	THYROID SCAN	EKG	EEG	AEP** VEP
INFANT DAY 2														

* *NON STRESS TEST; CONTRACTION STRESS TEST* * * *AUDITORY EVOKED POTENTIAL AND VISUAL EVOKED POTENTIAL*

FIG. 4. *Longitudinal flow sheet of maternal thyroid function tests during pregnancy, labor, and delivery and newborn thyroid evaluation on day 2. Measurements of amniotic fluid (AF) concentrations are of research interest but have not accurately reflected fetal thyroid status in utero.*

In normal uncomplicated pregnancies the fetal heart rate is in the range of 120–150 beats/min. In infants at risk for in utero hypothyroidism secondary to PTU administration or uncontrolled or untreated thyrotoxicosis, the heart rate may be abnormally slow or fast. Abnormal fetal heart rates can be detected by auscultation or external monitoring. Figure 5 (left) shows a fetal heart rate of 180/min during a nonstress test on a mother with a fetus with Graves' disease in utero. Congenital hyperthyroidism was confirmed at birth. In contrast, Figure 5 (right) depicts fetal bradycardia (120/min) in the hypothyroid fetus of a mother who was receiving 300 mg of PTU/day. At birth, bone age was retarded, cord serum T_4 was depressed, and TSH was elevated. These simple measurements are useful because maternal serum and AF levels of thyroid hormones and TSH do not accurately reflect fetal thyroid status in utero.

The clinical significance of hypo- or hyperthyroxinemia in utero and during the early neonatal period is unknown. Montoro and Mestman[20] have reported that among 19 untreated cases of maternal Graves' disease with hyperthyroidism there were 15 premature deliveries, 5 perinatal deaths, and 5 cases of serious neonatal morbidity. Children who were hyperthyroid in utero may present at a later age with subtle defects of the central nervous system and short stature.[12]

Labor and Delivery

The major obstetric risk for women with untreated or uncontrolled Graves' disease is the onset of premature labor. This compli-

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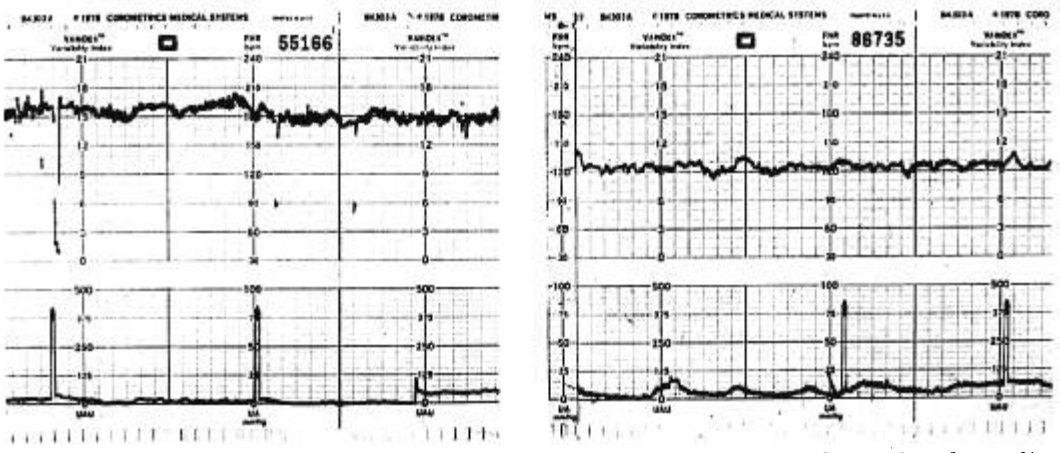

FIG. 5. *Fetal heart rate tracings obtained by an external monitor.* Left, *fetal tachycardia with a rate of 180/min in a fetus with in utero Graves' disease.* Right, *fetal bradycardia with a rate of 120/min in a mildly hypothyroid fetus whose mother was receiving 300 mg PTU/day.*

cation is less frequent in women who are euthyroid. Prolonged gestations (>42 weeks) have been observed in women who were hypothyroid because of antithyroid drugs or previous treatment with surgery or ^{131}I. The use of beta agonists to stop premature labor is contraindicated in patients who are hypermetabolic. In premature infants with congenital Graves' disease, lung maturation is accelerated along with skeletal development, and respiratory distress syndrome is rare.

Thyroid storm or crisis is an infrequent complication during pregnancy, labor, or delivery unless Graves' disease has not been suspected or treated. It may also occur with infections or surgical stress. Management of this problem is the same as in nonpregnant women, except that cesarean section delivery of the infant may be precipitated by fetal distress.

Evaluation of the Newborn Infants of Mothers With Graves' Disease or Chronic (Hashimoto) Thyroiditis

The metabolic outcome of infants of mothers with Graves' disease is not known in advance. In addition, the physical appearance of the child may indicate neither abnormal thyroid function nor the transient metabolic changes that can occur in the neonatal period. Table 4 shows infants at risk for abnormal thyroid function at birth and a suggested plan for their neonatal assessment. In addition to congenital Graves' disease, potential problems include iatrogenic neonatal hypothyroidism following administration of ^{131}I, I^-, PTU, methimazole or lithium to the mother. Maternal Hashimoto's disease may result in neonatal hyper- or hypothyroidism.

A careful physical examination should be done immediately after delivery for signs of hypo- or hyperthyroidism. Exophthalmos may not be apparent at birth, and a palpable thyroid gland (goiter) may be noted only when the head is hyperextended. Cord blood serum T_4 and TSH levels should be measured promptly because they reflect in utero thyroid status and the results are available more rapidly than those obtained by routine neonatal screening. These tests should be repeated on day 2 of life because transient, mild congenital hypothyroidism, secondary to low doses of maternal antithyroid drugs, is likely to be gone by then, or, if persistent, to require further observation and treatment. In infants of mothers who have received antithyroid drugs, neonatal hyperthyroidism may not be apparent until age 7–10 days.

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TABLE 4. Infants at Risk for Abnormal Thyroid Function at Birth

Maternal Diagnosis	Cord	Neonatal Assessment: Infant at Birth	Neonatal Assessment: Infant Age 2–7 Days
Infant at risk for congenital hyperthyroidism 1. Graves' disease with hyperthyroidism and Rx with PTU, methimazole, ^{131}I, or iodides 2. History of Graves' disease 3. Hashimoto's disease	T_4, TSH TSAb	1. Physical examination for IUGR*, goiter exophthalmos, tachycardia, bradycardia, size of anterior fontanel, synostosis, congenital anomalies 2. Gestational age by dates, ultrasonography during pregnancy, Dubovitz examination 3. Plot intrauterine growth by gestational age 4. Neurological examination 5. Bone age (knee) 6. Selected cases: EKG, EEG, auditory and visual evoked potentials, motor conduction velocity tests, skull x-rays	1. T_4, T_3, TSH, TSAb (If available) Normal → No Rx observe and repeat T_4, T_3, TSH 7–10 days Hypo → Repeat T_4, TSH Rx if abnormal at 7–10 days Hyper → Start Rx with PTU, Propranolol Lugol's
Infant at risk for congenital or early childhood hypothyroidism 1. Hashimoto's disease 2. ? Acute (subacute) thyroiditis 3. Familial genetic defect in thyroxine synthesis 4. Rx with iodides or lithium for nonthyroidal illness 5. Exposure to ^{131}I in utero	T_4, TSH ThyAb		1. T_4, T_3, TSH, ThyAb 2. Thyroid scan if hypothyroid Normal, no Rx Hypo Rx with Synthroid

*Intrauterine growth retardation.

The unpredictable outcome of infants at risk for Graves' disease is illustrated by Figures 6–8. Figure 6 shows a 21-year-old mother with Graves' disease who had been hypothyroid for many years following a thyroidectomy at age 7. She was maintained on replacement thyroid therapy (Synthroid, 0.15 mg/day) throughout pregnancy. Her infant was born with florid Graves' disease and exophthalmos, which lasted 6 months. The child is normal at age 20 months.

Figure 7, left, is a 38-year-old euthyroid mother with a history of Graves' disease and a remission following treatment with ^{131}I. She received no medication during pregnancy. A normal euthyroid infant was born

FIG. 6. Left, *hypothyroid 21-year-old mother who developed Graves' disease at age 7 and was treated by subtotal thyroidectomy. She was maintained on Synthroid, 0.15 mg, throughout pregnancy.* Center, *infant baby girl was born at term with severe Graves' disease, goiter, and exophthalmos, which persisted for 6 months.* Right, *normal child at age 20 months.*

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FIG. 7. Left, *euthyroid 35-year-old mother with a history of Graves' disease and treatment with ^{131}I and her normal newborn infant.* Right, *mother with onset of Graves' disease during pregnancy. She received 150 mg PTU/day from second trimester until delivery. Her child was born at term with congenital hypothyroidism, which was still present at age 10 days and required replacement therapy.*

at term. Figure 7, right, shows a mother who developed Graves' disease with exophthalmos during pregnancy. She was treated with only 50 mg of PTU 3 times a day for the last two-thirds of her pregnancy. Her term infant was born with congenital hypothyroidism with a delayed bone age, serum T_4 on day 2 of 3.2 μg/dl, and TSH of 97 μU/ml. At 6 days his T_4 level was 2.4 μg/dl, his TSH level was 100 μU/ml, and by 10 days of age the T_4 value had decreased to 1.4 μg/dl. The infant was started on replacement thyroid therapy, which was continued for 1 year. Six months after stopping the medication, he has normal thyroid function tests and a normal developmental evaluation.

We have observed the onset of neonatal and early-childhood-onset Graves' disease in only one child of two sets of monozygotic twins born to mothers with Graves' disease and hyperthyroidism during pregnancy. Figure 8, left, shows the C twins at age 6 years. Twin 1 on the left walked 3.5 months before her sister and throughout early childhood was noted to be hyperactive and to perspire profusely. On examination at age 6.5 years, both twins had a small goiter. Twin 1 was shorter and weighed less. She had a normal serum T_4 value but an elevated level of serum T_3. A TRH stimulation test was normal. Thyroid function tests were normal in twin 2.

Figure 7, right, shows the M twins of a hyperthyroid mother with Graves' disease who received 150–300 mg of PTU daily throughout pregnancy. Cord serum TSH levels were elevated, which indicated in utero hypothyroidism. Twin 1 developed

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mild neonatal Graves' disease with tachycardia on day 3 and exophthalmos and elevated levels of serum T_3 at age 5 months. Figure 9 depicts the discordant tests of thyroid function in the M twins to age 5 months. The explanation for these metabolic differences in monozygous twins is not apparent but may represent genetic mosaicism.

Long-Term Assessment of Children Who Had Abnormal Thyroid Function in Utero

There is a paucity of information on the long-term outcome of children who have had untreated or overtreated Graves' disease in utero or in the early neonatal period. In addition, there are only a few reports of a small percentage of children whose mothers have received variable doses of antithyroid drugs or a subtotal thyroidectomy at different periods of gestation.

Dussault et al.[29] have reported the effects of neonatal hyperthyroidism on the development of the hypothalamic-pituitary-thyroid axis in the rat. Their data indicated that neonatal hyperthyroidism was associated with a permanent reduction in body weight in both male and female rats. They also observed a delay in the attainment of peak concentrations of hypothalamic TRH and pituitary and serum TSH. Serum T_4 and T_3 concentrations were significantly and permanently reduced in animals with neonatal hyperthyroidism, which suggested a permanent resetting of the regulatory set-point for pituitary TSH secretion and increased sensitivity to the feedback inhibitory effects of thyroid hormones.

Hollingsworth et al.,[12] in an 11-year follow-up of 26 pregnancies in 20 women with Graves' disease, found that 27% of 24 surviving children had persistent neurologic problems with complications of synostosis, perceptual motor difficulties, or

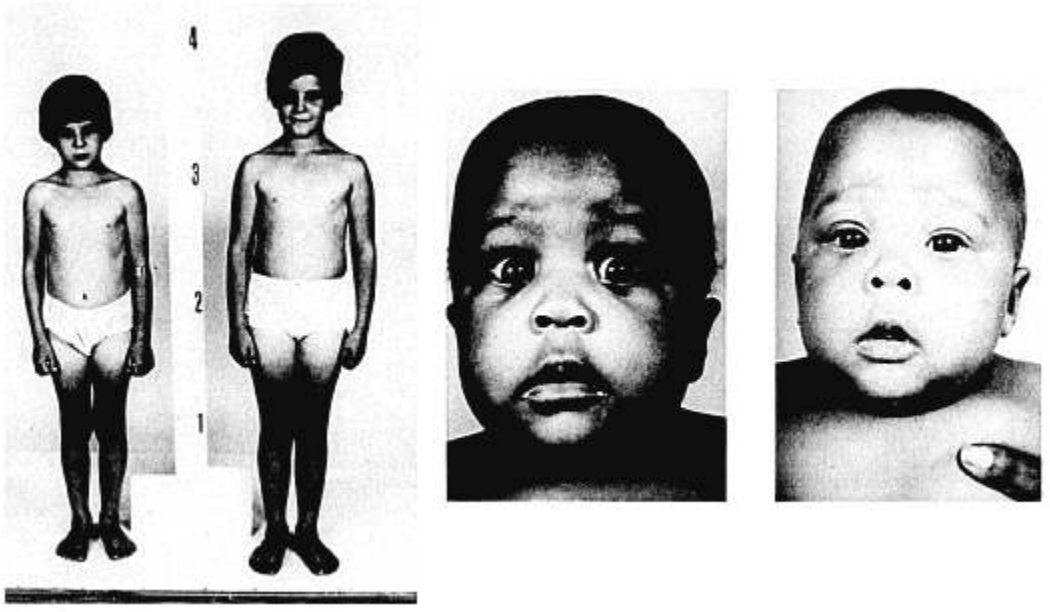

FIG. 8. Left, *monozygotic C twin girls at 6.5 years. Both twins have goiters, and twin 1* (left) *has elevated levels of serum T_3, symptoms of hyperthyroidism and decreased growth.* Right, *monozygotic twins of a 25-year-old mother who developed severe Graves' disease during pregnancy. Twin 1* (left) *had mild neonatal Graves' disease, but Twin 2 was euthyroid.*

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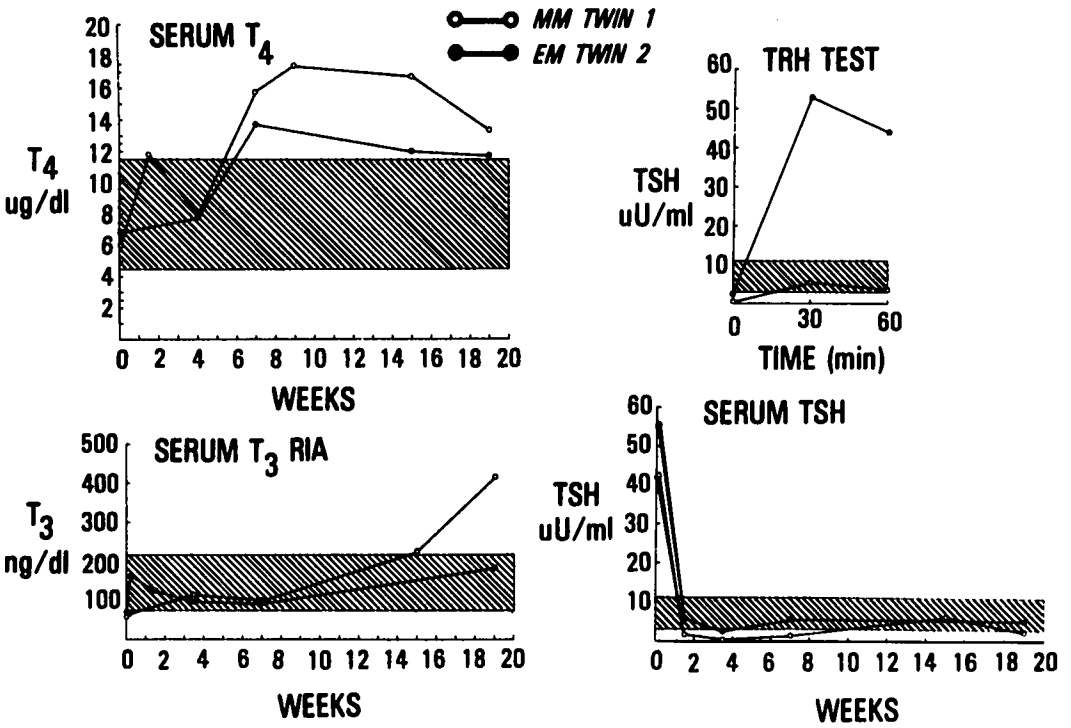

FIG. 9. *Serum T_4 (*upper left*), T_3 (*lower left*) and TSH values in the M twins from birth (O, cord blood) to age 5 months. A TRH test with 100 μg TRH was performed at age 1 month. Twin 1 had neonatal hyperthyroidism with elevated levels of serum T_4 to age 5 months; increased serum T_3 values at 5 months, and failure of TSH response to TRH at 1 month.*

severe hyperactivity even when euthyroid. Eleven children (42%) were not growing well with height and weight below the 10th percentile. Eight children were of school age but below grade level.

The fetus of a mother with Graves' disease treated with PTU is at risk for either hypo- and hyperthyroidism in utero and during the neonatal period. Since both conditions may cause potentially permanent alterations in the maturation of the brain, it is recommended that all such children have long-term assessment of their growth, development, intellectual, and psychological maturation. Table 5 outlines suggestions for follow-up until school age. It will also be of interest to observe the timing of puberty, later evaluation of the hypothalamic-pituitary-thyroid axis, and prevalence of thyroid disorders in this unusual group of children.

TABLE 5. Long-Term Assessment of Children With Abnormal Thyroid Function in Utero

I. Newborn period
   1. Physical examination, including assessment of gestational age and neurologic examination
   2. Bone age (knee). Skull x-rays if synostosis, marked frontal bossing or abnormally large or small anterior fontanel is present
   3. Procedures of special interest in selected cases: auditory and visual evoked potentials, motor conduction velocity tests, EKG, EEG, CAT scan of orbit and skull
   4. Reexamine and repeat thyroid function tests (T_4, TSH, T_3) at 1-3-6 weeks

II. Early childhood (6 weeks to 2 years)
   1. Usual pediatric care
   2. Developmental evaluation and thyroid function tests at 6, 12, 18, 24 months
   3. Plot growth curve for height and weight

III. Age 2-6 years
   1. Annual physical examination, growth measurements
   2. Thyroid function tests if there are signs or symptoms of thyroid disease, or changes in pattern of growth
   3. Preschool developmental, psychologic, IQ, and hearing tests

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Conclusion

Pregnancy in women with Graves' disease creates an experiment of nature with a serious possibility for harm to the fetus, the newborn infant, and perhaps the lifelong intellectual potential of the individual. Since maternal risk is minimal and both medical and surgical therapy can be accomplished easily in a skillful manner, the primary goal of each therapeutic medication or procedure in the antenatal and neonatal periods should focus primarily on the risk versus the benefit to the fetus and infant. Thus, the obstetrician assumes the role of a pediatrician for the unborn child.

For women with thyroid disorders or a family history of autoimmune thyroid disease (Graves' disease or Hashimoto's thyroiditis), preconception counseling by an endocrinologist and, in some cases, a geneticist may be extremely helpful. Women with Graves' disease who wish to become pregnant should receive definitive treatment for hyperthyroidism before conception, if possible, in order to avoid the necessity for medication or surgery during gestation. The use of therapeutic doses of ^{131}I to women of childbearing age is controversial. Women with a history of previous but treated Graves' disease should be observed carefully for hypothyroidism, pregnancy-associated exacerbation of hyperthyroidism, or signs of in utero Graves' disease in their fetus. In those individuals who are hyperthyroid when conception occurs or become so with the metabolic stress of pregnancy, prenatal care should be obtained in a setting where joint supervision is possible with an endocrinologist familiar with antenatal thyroid disorders, a perinatologist, and a pediatrician.

Although the cause of Graves' disease is unknown, it represents an autoimmune genetic disorder with a predilection for women. Thyroid stimulatory antibodies (TSI and TSAb) are useful markers during pregnancy because they are IgG immunoglobulins that traverse the placenta and may stimulate the fetal thyroid. It is not clear why in all infants at risk, such as monozygotic twins and infants of some mothers with high titers of TSAb, in utero or neonatal Graves' disease does not develop. Rarely will an infant from a family with many generations of Graves' disease, but with an unaffected mother, be born with the disorder. In addition, there is no explanation at present for the children who experience persistent Graves' disease for many years after birth and long beyond the expected dissipation of placentally transported TSAb. Until the pathogenesis of Graves' disease can be defined in individual families and pregnant women with hyperthyroidism, careful clinical, immunologic, and genetic observations of each mother-infant pair will be invaluable.

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