

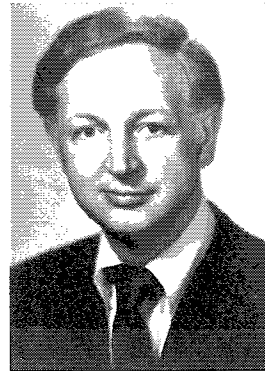
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HYPERTHYROIDISM IN PREGNANCY

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Hyperthyroidism in Pregnancy

The classical clinical features of hyperthyroidism such as goiter, tachycardia, heat intolerance, diaphoresis and nervousness may all occur in euthyroid pregnant women. Because of this, hyperthyroidism is a more difficult disease to diagnose clinically in a pregnant woman. Problems in making the clinical diagnosis are compounded by changes in thyroid function tests during pregnancy which make the laboratory diagnosis difficult. Even after the diagnosis is made, the decision about therapy must also take the presence of the fetus into account.

There is no convincing evidence that impaired fertility is a major problem in mild to moderate hyperthyroidism. There is also disagreement as to whether fetal mortality is increased once the pregnancy is established. Part of the disagreement stems from the fact that hyperthyroidism in pregnancy is uncommon. In a study of 38,381 pregnant women, 75 were found to have thyrotoxicosis.¹ The small number of pregnant women with thyrotoxicosis, despite the size of the study, precludes definite conclusions. Hyperthyroidism was apparently associated with a slight increase in neonatal mortality and a significant increase in the frequency of low birthweight infants. The balance of evidence indicates that mild or moderate hyperthyroidism is not harmful to the continuation of the pregnancy, nor is there evidence that pregnancy makes the thyrotoxicosis more difficult to control. In fact, pregnant women appear to tolerate mild forms of hyperthyroidism without difficulty. During the postpartum period, however, there does seem to be a tendency for the thyrotoxic patient to

relapse. Thyrotoxicosis has been suggested to occur more frequently during gestation, but this impression may be due to the fact that young women are rarely seen by physicians until they reach the obstetrician when the diagnosis is made.

Laboratory Diagnosis

To understand the difficulties in laboratory diagnosis, it is necessary to review normal thyroid physiology during pregnancy. Early work indicated that the basal metabolic rate (BMR) during pregnancy was elevated, and it was suggested that thyroid function was increased during pregnancy. Subsequent studies have shown that 80% of this increase in BMR can be accounted for by the fetoplacental unit, while increased work of the maternal heart accounted for the rest.² The impression that thyroid function was increased during normal pregnancy was heightened when serum thyroid hormone levels were found to be elevated during normal pregnancy. The hormone values increased to a plateau by the end of the first trimester that was approximately twice the nonpregnant value. The increased serum thyroid hormone concentrations during pregnancy were subsequently found to be due to an increase in serum thyroxine binding globulin (TBG) which was stimulated by the increased estrogens. Since the resin triiodothyronine uptake test (RT₃U) depends on the unsaturated binding capacity of TBG, the test is also altered during normal pregnancy (Fig. 1). Although there is an increase in the amount of thyroxine (T₄) and triiodothyronine (T₃) bound to TBG, the increase in the binding capa-

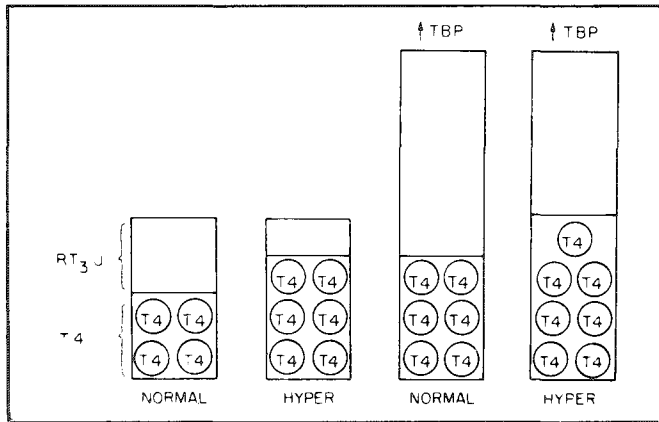


Figure 1

Thyroid hormone is transported in the serum by thyroxine binding protein (TBP) of which the major protein is thyroxine binding globulin (TBG). In a normal euthyroid patient, a number of the binding sites of TBP are saturated by thyroid hormone. The unsaturated binding sites form the basis for the resin T_3 uptake test (RT_3U). When TBP is increased as TBG in pregnancy, more thyroxine is found, and the unsaturated binding sites are also increased. Because of these changes the diagnosis of hyperthyroidism in pregnancy may be more difficult.

city is greater still, and the RT_3U will be in the hypothyroid range. This combination of an elevated serum thyroxine concentration and a RT_3U in the hypothyroid range is characteristic of pregnancy and other states with elevated estrogens. Because of the danger of radiation to the fetus, the radioactive iodine thyroid uptake is absolutely contraindicated in pregnancy. However, the uptake is elevated in pregnancy, probably due to a relative iodine deficiency.^{3, 4}

Serum T_4 concentrations above $13\mu\text{g}/100\text{ ml}$ are suggestive of thyrotoxicosis. Similarly a RT_3U in the euthyroid range during pregnancy is indicative of hyperthyroidism provided that the patient does not have a deficiency of TBG. The combination of a high serum T_4 concentration and a normal RT_3U is suggestive of thyrotoxicosis during pregnancy. The product of these determinations yields the free thyroxine index which theoretically should be proportional to the free thyroxine concentration. There is evidence, however, that the free thyroxine index may not always be an accurate measure of the free thyroxine concentration during pregnancy⁵ as determined by equilibrium dialysis (Fig.2).

Figure 2

Changes in Thyroid Function During Pregnancy

- Increased: — I^{131} Thyroid Uptake
- BMR
- T_4 , T_3 , TBG
- TSH, hCT (human chorionic thyrotropin)
- TSH response to TRH (thyrotropin-releasing hormone)
- Normal: — Free T_4 Concentration
- T_4 Production Rate

Clinical Diagnosis

As mentioned previously, the clinical diagnosis of thyrotoxicosis during pregnancy can be very difficult. Signs of hyperthyroidism such as weight loss may be obscured by the normal weight gain of pregnancy. Toxic nodular goiter or Plummer's disease is uncommon during the childbearing period, and toxic diffuse goiter (Graves' disease) is by far the most common form of hyperthyroidism seen in pregnancy. The eye signs of Graves' disease, including stare, lid lag and exophthalmos, may be helpful in the initial diagnosis. These same signs may occur, however, in euthyroid patients with Graves' disease. Muscle wasting, particularly in the quadriceps, and onycholysis or separation of the distal nail from the nail bed are helpful diagnostic signs. A resting pulse rate above 100 beats per minute may also be helpful in making the clinical diagnosis of thyrotoxicosis in the pregnant woman.

Therapy With Propylthiouracil

Perhaps because hyperthyroidism is relatively uncommon during pregnancy, controversy continues about optimal medical therapy. Radioactive iodine therapy has no place in the treatment of the pregnant thyrotoxic woman. The dispute rests between a medical as opposed to a surgical approach, and further, there is disagreement about the optimal form of medical therapy.

Regardless of whether the decision is made to operate, the pregnant thyrotoxic woman must first be controlled with antithyroid medication. Since propylthiouracil and methimazole block the synthesis and not the release of thyroid hormone from the gland, a clinical response to drug therapy does not occur until the stored thyroid hormone is utilized. The time required to achieve control of the thyrotoxicosis will therefore depend in part on the amount of colloid present in the thyroid gland. Recent evidence has indicated that elevated serum T_3 concentrations fall more rapidly during propylthiouracil (PTU) therapy,⁶ because PTU blocks the peripheral conversion of T_4 to T_3 . Furthermore, methimazole therapy has been associated with scalp defects in the offspring of treated mothers. Therefore, PTU would seem to be preferable for the therapy of hyperthyroidism during pregnancy.

The patient may notice some clinical improvement after the first week of therapy and may approach the euthyroid state after four to six weeks. PTU has a short duration of action and the drug is usually given in divided doses. Although the majority of patients might be maintained on once a day dosage, some patients may require the drug every eight hours or even more frequently for adequate control of the thyrotoxicosis. Once the diagnosis of hyperthyroidism has been made, the pregnant woman should be started on 100 to 150 mg of PTU every eight hours. After control of the hyperthyroidism has been achieved as determined by a fall in the serum thyroxine concentration as well as an improvement in signs and symptoms, the dose of PTU can be decreased to 200 mg daily in divided doses. Serial serum T_4 determinations should be performed monthly during gestation.

An attempt should be made to use as low a dose of PTU as possible since there is some evidence to suggest that fetal goiter does not occur if the mother receives less than

100 mg of PTU per day.⁷ This is made easier by the fact that pregnant women seem to tolerate mild to moderate degrees of hyperthyroidism better than they do hypothyroidism. If thyrotoxicosis recurs after the dose is lowered, it should be raised again to 300 mg/day. Recurrences of the hyperthyroidism are particularly likely in the postpartum period, and the drug should be increased to 300 mg/day following delivery.

Complications of Therapy

The most common complications of PTU therapy include skin rash, pruritus, nausea and a metallic taste. If a drug reaction occurs with PTU, it may be possible to continue therapy with methimazole, despite the previous reservations, since there is not a high degree of cross-reactivity. The development of agranulocytosis, however, is an immediate indication to stop all antithyroid agents. In fact, the patient should be instructed to stop antithyroid medication with the development of fever or sore throat and to report to her physician for a leukocyte count. A leukocyte count obtained before institution of therapy will be most helpful since about 10% of patients with Graves' disease may have leukopenia prior to therapy.

A major problem with PTU therapy in pregnancy is that PTU crosses the placenta and may cause fetal goiter. The goiter itself is not large and unlike iodide-induced fetal goiters is virtually never obstructive. Rather, there is the implication that the fetus was hypothyroid during a critical period in brain development. The goiter is thought to be due to the inhibition of fetal thyroid hormone production by PTU with a secondary elevation of fetal thyroid-stimulating hormone (TSH) secretion and production of the goiter (Fig. 3). Most children who have been exposed to antithyroid drugs in utero do not develop goiter. In those children who do not develop goiter, sufficient maternal hormone appears to be able to cross the placenta and shut off fetal TSH secretion.

The great majority of children who develop goiter secondary to PTU appear to have no subsequent ill effects from this drug, although there have been case reports of mental retardation. We compared intellectual and physical development of 15 children who had been exposed to PTU in utero and 18 siblings who had not been exposed.⁸ Although the sample was too small to make any definite conclusions, the data did not suggest that PTU therapy during pregnancy had an adverse effect on subsequent growth and development. Whether decreased maternal thyroid hormone is responsible for the development of neonatal goiter in offspring

EFFECT OF PTU ON FETAL THYROID FUNCTION

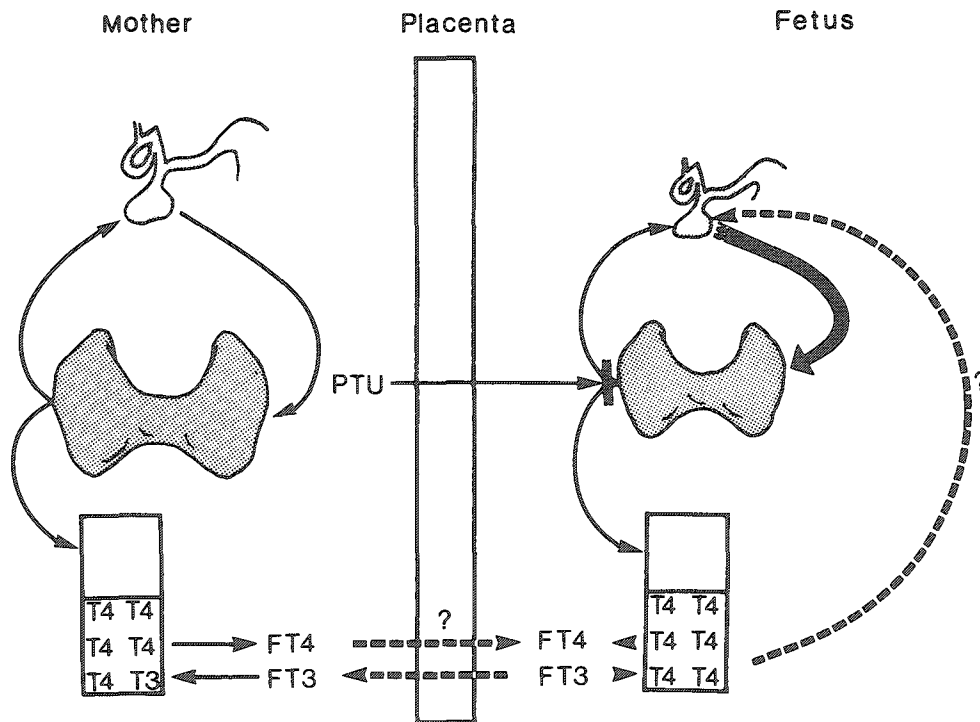


Figure 3

Propylthiouracil crosses the placenta without difficulty and in adequate concentrations will block the fetal thyroid gland. In response there will be an increase in fetal TSH stimulation unless adequate amounts of maternal hormone cross the placenta.

of women treated with PTU becomes important in assessing the need for thyroid hormone therapy during pregnancy. Some authors believe that the addition of thyroid hormone to the therapeutic regimen of PTU during pregnancy prevents fetal hypothyroidism and goiter formation. Certainly every effort should be made to avoid maternal hypothyroidism during pregnancy. If there is suspicion of hypothyroidism in a pregnant woman receiving PTU, the drug should be decreased or discontinued and thyroid hormone administered.

Even more important is the prevention of fetal hypothyroidism. The evidence, however, is less clear that this disturbing complication is prevented by the mother receiving the usual replacement doses of thyroid hormone. Both T_4 and T_3 cross the placenta with difficulty. The addition of thyroid hormone may increase the amount of PTU required to control the hyperthyroidism, and, as mentioned previously, there appears to be definite advantages in maintaining the pregnant woman on the lowest possible dose of PTU. If the pregnant woman on antithyroid medication can be evaluated at monthly intervals, with the avoidance of low serum T_4 concentrations, then thyroid hormone supplementation is probably unnecessary. Pregnant women with hyperthyroidism should be treated with the lowest effective dose of PTU. They appear to tolerate at least mild degrees of hyperthyroidism without great difficulty, and it is better to err on the side of undertreatment than overtreatment.

Propranolol

If the pregnant woman with thyrotoxicosis is unable to tolerate PTU or methimazole, she can be treated with the beta-adrenergic blocker, propranolol. Propranolol will decrease the tachycardia and other signs and symptoms of beta-adrenergic stimulation but does not significantly affect the increased metabolism. Recent evidence indicates that propranolol blocks the conversion of T_4 to T_3 and thus might have some effect on the metabolic rate.

Propranolol has been suggested as the primary treatment for hyperthyroidism during pregnancy because fetal goiter would not occur as a complication of therapy. Since propranolol does not significantly affect the increased metabolic rate, however, thyrotoxicosis is not really controlled but only masked. Beta-adrenergic stimulation suppresses uterine irritability, and the use of a beta-adrenergic blocker results in increased uterine irritability and occasionally premature labor. Furthermore, babies whose mothers have received propranolol have experienced intrauterine growth retardation and have been depressed at birth with low Apgar ratings.⁹ After delivery, they have had bradycardia and hypoglycemia. For these reasons propranolol should not be used as the prime drug for long-term therapy of thyrotoxicosis during pregnancy.

If it is necessary to control thyrotoxicosis in the pregnant woman rapidly, the combination of propranolol with iodides will usually result in marked improvement within two to seven days. Iodides have a twofold action: (1) inhibition of thyroid hormone release and (2) short-term inhibition of thyroid hormone synthesis. Iodides administered to mothers in doses as low as 12 mg daily have caused fetal goiters. Maternal ingestion of iodides appears to produce greater enlargement of the fetal thyroid, and iodide therapy

should not be prolonged during pregnancy. Once control of the thyrotoxicosis has been achieved, the patient may undergo subtotal thyroidectomy but the anesthesiologist should be aware that the patient has received beta-adrenergic blockers.

Surgery

Subtotal thyroidectomy has often been delayed until after the first trimester to avoid an increased possibility of spontaneous abortion. Spontaneous abortions do occur more frequently during the first trimester but there is no evidence to suggest that subtotal thyroidectomy is more hazardous at that time. Surgery during any trimester does present the added risk of fetal anorexia.

In addition some operative mortality is associated with any surgical procedure. There are two specific complications of thyroid surgery which are extremely difficult to treat: recurrent laryngeal nerve paralysis and hypoparathyroidism. These complications occur rarely but, when they do occur, they are disabling and difficult to treat. Unfortunately the complication rate for subtotal thyroidectomy rises as fewer operations are performed.

Some studies suggest that surgery is the treatment of choice. Thirty-three patients on whom subtotal thyroidectomies were performed suffered only one fetal loss, whereas in 30 pregnancies treated medically, there were four spontaneous abortions, two patients with thyroid storm and two cases of thyrocardiac failure.¹⁰ Although the data would appear to indicate that surgery is the treatment of choice, there is a definite bias in this kind of study. All patients were prepared for surgery with antithyroid drugs, and subtotal thyroidectomy was deferred until after the first trimester. Therefore, any patient who aborted during the first trimester was almost by definition a medical failure. Two patients who aborted while on antithyroid medication were being prepared for surgery. Similarly, patients who were in cardiac failure or thyroid storm were not considered candidates for surgery.

Since surgical complications do occur and since the majority of patients who receive PTU have uncomplicated pregnancies, medical therapy would seem to be the preferred treatment for hyperthyroidism during pregnancy. A reasonable therapy for the pregnant thyrotoxic woman would be to treat with as low a dose of PTU as possible, preferably under 100 mg a day. If there is any question of maternal hypothyroidism or an inability to closely monitor the patient with thyroid function tests, thyroid hormone should be added to the regimen. Triiodothyronine, 75 μ g/day, has certain theoretical advantages, but the serum thyroxine determination can no longer be used as a measure of thyroid function.

Thyroid Storm

Although hyperthyroidism presents a risk to the fetus, there is little danger to the mother except for the occurrence of thyroid storm. This rare but frightening complication is a life-endangering augmentation of the signs and symptoms of hyperthyroidism. Thyroid storm is more likely to occur when there is some precipitating factor such as infection, labor, or caesarean section. Thyroid storm is more com-



Figure 4

A 2,300 gm neonate born to mother with active Graves' disease with high titer of LATS. The baby also had a high titer of LATS as well as a goiter, congestive heart failure, hepatosplenomegaly and thrombocytopenia.

monly seen in patients in whom the diagnosis of hyperthyroidism has been unsuspected, although it also occurs in inadequately controlled patients. If the diagnosis of hyperthyroidism is considered in the pregnant woman and therapy begun, this frightening complication of thyrotoxicosis should be virtually eliminated.

Neonatal Thyrotoxicosis

Hyperthyroidism occurring in the newborn is even more uncommon than in the mother. The presence of goiter, exophthalmos, and tachycardia in a nervous, hyperirritable infant with an elevated serum thyroxine level is sufficient to make the diagnosis with a reasonable degree of certainty. The occurrence of neonatal thyrotoxicosis is clearly associated with high levels of thyroid-stimulating immunoglobulins in the maternal serum (Fig. 4). The neonatal serum also contains thyroid-stimulating immunoglobulin which has crossed the placenta and which disappears as the baby becomes euthyroid. A number of these children have been considered to be premature because of low birthweight. On the basis of bone age, however, these children actually appear to have accelerated maturity secondary to the increased thyroid hormone.

If thyroid-stimulating immunoglobulin causes neonatal thyrotoxicosis as well as maternal Graves' disease, it is surprising that more instances of neonatal thyrotoxicosis are not recognized. One reason may be that transplacental passage of PTU inhibits the clinical expression of hyper-

thyroidism in the newborn. As a consequence, thyrotoxicosis may not become evident clinically for five to ten days in infants exposed to PTU in utero. Other factors may also play a role; contrary to the general trend of thyroid disease, neonatal thyrotoxicosis occurs more commonly in males. A reasonable approach would be to obtain serum long-acting thyroid stimulator (LATS) levels on all pregnant women with Graves' disease. LATS levels are frequently correlated with the titer of the thyroid-stimulating immunoglobulins (TSI) to be responsible for Graves' disease.

REFERENCES

1. Niswander KR, Gordon M, Berendes HW: *The Women and Their Pregnancies*. Philadelphia, WB Saunders Co, 1972.
2. Burwell CS: *Bull of the Johns Hopkins Hosp* 95:115, 1954.
3. Halnan KE: *Clin Sci* 17:281, 1958.
4. Crooks J, Tulloch MT, Turnbull AC, Davidsson D, Skulason T, Snaedel G: *Lancet* 2:625, 1967.
5. Souma JA, Niejadlik DC, Cottrell S, Rankel S: *Am J Obstet Gynecol* 116:905, 1973.
6. Larson PR: *Metabolism* 20:609, 1971.
7. Burrow GN: in Burrow GN, Ferris TF (eds): *Medical Complications During Pregnancy*. Philadelphia, WB Saunders Co, 1975.
8. Burrow GN, Bartsocas C, Klatskin E, et al: *Am J Dis Child* 116:161, 1968.
9. Gladstone GR, Hordof A, Gersony WM: *J Pediatr* 86:962, 1975.
10. Hawe P, Francis HH: *Brit Med J* 2:817, 1962.