Hyperthyroidism and Pregnancy *

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HYPERTHYROIDISM is infrequently associated with pregnancy, but the combination is of interest and importance because uncontrolled thyrotoxicosis can be a major hazard for the pregnant woman and her developing fetus. A review of the literature concerning this association reveals a diversity of opinion as to its incidence, the effect of hyperthyroidism on pregnancy, the influence of pregnancy on the development and course of hyperthyroidism, the effect of maternal thyrotoxicosis and its treatment on the fetus, and the appropriate treatment of hyperthyroidism occurring during pregnancy. Our purposes in the present report are to discuss certain of these controversial issues, and to review the experience in this connection at the Charity Hospital during the past 16 years.

Material

There were 30 thyrotoxic women among 152,084 pregnant patients observed at the Charity Hospital in New Orleans during the 16-year period, 1943–1958. The ages of the patients varied from 18 to 42 years; a mean of 32 years. Twenty-seven were multiparas, and 3 were primiparas. Twenty-seven were colored, and 3 were white; a racial distribution similar to that seen in the Charity Hospital general obstetrical population during the period under study. Eighteen of the 30 patients experienced the onset of thyrotoxic symptoms during pregnancy; 12 during the first trimester, one in the second trimester, and five in the third trimester. Symptoms antedated the pregnancy in 12 patients. Twenty patients had toxic diffuse goiter (5 of them recurrent), and ten had toxic nodular goiter. The clinical severity of the thyrotoxicosis was considered to be mild in eight cases, moderate in 17 and severe in five. The mean basal metabolic rate was + 60 per cent. Radioactive iodine uptake studies in 13 patients gave values ranging from 35 per cent to 100 per cent, with a mean value of 75 per cent (35 per cent being considered the upper limit of normal in this laboratory). Protein bound iodine values in the few patients studied ranged from 11.3 to 22 micrograms per cent (normal range in this laboratory is from 5 to 8 mcg. per cent in nonpregnant women).

Treatment and Results

Only eight thyroidectomies were performed during pregnancy; five during the first trimester and three during the second trimester. Preoperative control of the hyperthyroidism was accomplished with propylthiouracil and Lugol's solution in seven cases, and iodine and sedation in one. Thyroidectomy had no demonstrable adverse effect upon these eight pregnancies, seven of which resulted in normal infants. One patient who had been operated upon during the first trimester developed a severe toxemia of pregnancy during the third trimester and had a term stillbirth.

Twenty-two thyrotoxic women were not operated upon while pregnant. Twenty of them were managed by the use of antithyroid drugs alone, and two received only iodine and sedation. Six of the 22 patients had thyroidectomy relatively soon after delivery. Of the remaining 16, four are pres-

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ently awaiting thyroidectomy, five refused operation and are being continued on propylthiouracil, four apparently had drug-induced remissions of their thyrotoxicosis, and three were lost to follow up.

In the group of 22 patients treated without operation, three abortions occurred prior to institution of therapy but after thyrotoxicosis had become manifest. While receiving propylthiouracil three patients aborted and two had term stillbirths. Abnormalities observed in the 14 infants born alive to mothers whose hyperthyroidism had been treated by antithyroid drugs alone included a small goiter which subsided without treatment, a persistent goiter in a cretin, and a huge hyperplastic thyroid which produced tracheal compression and death a few minutes after birth.

Thus, a total of 42 pregnancies occurred in 30 patients during the course of their thyrotoxicosis. Thirty-three living babies were produced; 32 of which survived, and 31 have developed normally. This represents a fetal loss of 24 per cent.

Discussion

The reported incidence of hyperthyroidism among pregnant women ranges from 0.02 per cent to 3.7 per cent, with an average of about 0.2 per cent.[21] The incidence of pregnancy in patients with thyrotoxicosis has been recorded as varying from 0.4 per cent to 3 per cent.[15] At the Charity Hospital in New Orleans the incidence of hyperthyroidism during pregnancy is 0.02 per cent.

The extent to which an associated pregnancy may increase the difficulty of diagnosis of hyperthyroidism has been emphasized in the literature. During normal pregnancy the thyroid may undergo considerable enlargement, and occasionally the goiter is of sufficient size to produce pressure symptoms. Emotional instability, tremor and tachycardia occur in many normal pregnant women, and when an enlarged thyroid of pregnancy is discovered in addition to these symptoms, a diagnosis of thyrotoxicosis may be made too readily. The diagnosis of hyperthyroidism during pregnancy is primarily a clinical one, because the conventional laboratory tests are less reliable under these circumstances. The basal metabolic rate, serum protein bound iodine, radioactive iodine uptake and serum cholesterol levels increase during normal pregnancy.[24]

Conflicting opinions have been expressed concerning the effect of thyrotoxicosis on pregnancy. It has been suggested that uncontrolled hyperthyroidism is accompanied by an unusually high incidence of abortions, premature births and toxemias.[1, 9, 14, 18] Others contend that these complications are not more frequent in the presence of hyperthyroidism than in normal pregnancy.[4, 5, 21]

Six of the 42 pregnancies experienced by the 30 thyrotoxic women in our series ended in spontaneous abortion. Three of the abortions occurred in patients who had not yet sought medical treatment of the hyperthyroidism. Three abortions and two term stillbirths occurred in patients under treatment with antithyroid drugs. One of the three women with toxemia of pregnancy had been rendered euthyroid by thyroidectomy during the first trimester, but developed a severe toxemia in the third trimester and delivered a term stillborn.

Javert[14] reported an incidence of toxemia of pregnancy associated with hyperthyroidism of 77 per cent at the New York Hospital; while at the Mayo Clinic, Brandes[2] found no increase in toxemia of pregnancy among 75 patients with hyperthyroidism. Three of the 42 pregnancies in our series, or 7 per cent, were complicated by toxemia. The incidence of toxemia of pregnancy in the Charity Hospital general obstetrical population is 18 per cent.

While opinion is divided as to the effect of thyrotoxicosis on the incidence of abortions, stillbirths, toxemias and certain other complications of pregnancy, there is general agreement that prompt control of the hyperthyroidism will tend to eliminate

whatever influence this factor may have on the incidence of such complications.

The effect of pregnancy upon hyperthyroidism is also debatable. Most authors [1, 5, 21] believe that pregnancy usually does not influence the course of hyperthyroidism. Falls,[7] Gardiner-Hill [9] and Javert [14] contend that in some instances pregnancy may actually exert a beneficial effect on thyrotoxicosis. Clute and Daniels [4] feel that pregnancy is a major additional burden to the thyrotoxic patient. There appears to be no conclusive evidence that pregnancy is an important factor in the etiology of hyperthyroidism.

While there is also lack of agreement concerning the effect of hyperthyroidism on the developing fetus, the weight of evidence would appear to support the belief that thyrotoxicosis per se probably does not harm the fetus.[4, 5, 21] Of 15 pregnant women treated by thyroidectomy by Clute and Daniels,[4] 14 delivered normal living infants and one had a miscarriage. Dailey and Benson [5] reported 21 cases of hyperthyroidism complicating pregnancy and of the 14 patients who went to term 13 delivered normal babies, and there was one stillborn.

Pregnancy does not greatly complicate the treatment of hyperthyroidism if it is remembered that (1) the administration of radioactive iodine is contraindicated, (2) the induction of hypothyroidism is to be avoided, and (3) thyroidectomy can be carried out without undue risk to mother or fetus.

Radioactive iodine should not be administered to the pregnant woman because the isotope traverses the placenta and is picked up by the fetal thyroid.[3, 13] Embryonic thyroid tissue appears to have a much greater relative avidity for the radioactive material than does the maternal thyroid.[23] Russell and associates [23] administered large doses of I^{131} to 2 pregnant women with thyroid carcinoma, and both delivered infants with congenital hypothyroidism. One of the babies died at the age of 3 months, and no thyroid tissue could be found at postmortem examination. Valensi [25] reported the occurrence of cretinism in an infant born to a young woman whose hyperthyroidism had been treated with I^{131} early in the second trimester.

Although certain studies seem to indicate that the human fetal thyroid does not collect administered radioactive iodine during the first 12 weeks of life,[3, 13] and it has been suggested that during the first trimester the pregnant woman may receive therapeutic doses of I^{131} without danger of retention of the radioactive material by the fetus,[3] it is our opinion that pregnancy should continue to be regarded as a contraindication to the use of radioactive iodine. Also, the ages of the pregnant patient and her fetus are such as to make the use of I^{131} undesirable because of its possible future carcinogenic effect on the maternal and fetal thyroids, and the possibility of mutation of genes resulting from gonadal irradiation.

Antithyroid drugs also cross the placental barrier and may affect the fetal thyroid.[1, 8, 10, 11, 12, 16, 19, 22] The administration of thiouracil to pregnant rats and guinea pigs produces enlargement and hyperplasia of the thyroid gland and retarded growth in the offspring, abnormalities which soon disappear when the drug is discontinued.[8, 10, 12] The fact that these fetal abnormalities can be prevented by the concurrent administration of thyroid hormone to the mothers suggests that it is thiouracil-induced hypothyroidism and not the thiouracil itself which is harmful to the fetus.[1]

Krementz and associates [19] recently reviewed the literature concerning the effect on the fetus of the maternal administration of antithyroid drugs. They were able to collect 57 cases of infants which showed no abnormality attributed to the antithyroid drugs administered to the mother during pregnancy; but recorded 18 cases (16 collected and two of their own) in which abnormalities in the infant were thought to be due to antithyroid therapy given to the mother. Included among these infant abnormalities were mild transient goiter, se-

vere hypothyroidism, abortion, delayed ossification, retarded growth and thyroid hypertrophy sufficient to cause tracheal compression and death. It should be emphasized that in most instances the complications were mild and transitory, and also that they might have been prevented by the administration of desiccated thyroid concomitantly with the antithyroid drug.

In 1950, Bell [1] demonstrated, in a series of 21 pregnant patients with thyrotoxicosis, that the thiouracil drugs could be safely and effectively used to prepare such patients for thyroidectomy. It was his opinion that maternal hypothyroidism was accompanied by an increased incidence of toxemia of pregnancy, abortion and fetal abnormalities; and that induced hypothyroidism could be prevented by avoidance of overdosage of antithyroid drugs and the concomitant use of desiccated thyroid. It is of interest that the three cases of goiter in the newborn observed in our series occurred in infants whose mothers had been rendered hypothyroid by excessive amounts of propylthiouracil. One of these women received small doses of desiccated thyroid during the last weeks of pregnancy; but her hypothyroidism was not corrected, and she delivered an infant which died a few minutes after birth of tracheal compression by a massive hyperplastic goiter.*

The extensive literature concerning the treatment of hyperthyroidism associated with pregnancy is controversial, but most authors [1, 4-6, 18-21] favor subtotal thyroidectomy after adequate medical preparation with antithyroid drugs and/or iodine. Since the antithyroid drugs traverse the placenta and occasionally affect adversely the fetal thyroid, when possible the use of iodine alone for preoperative preparation seems desirable. Prompt and complete control of the more severe degrees of thyrotoxicosis complicating pregnancy can best be achieved with antithyroid drugs, with the concomitant administration of desiccated thyroid and iodine to minimize the possibility of fetal abnormality secondary to drug-induced maternal and fetal hypothyroidism. The risk of thyroidectomy is also increased by the presence of myxedema. Since many patients have hypothyroidism for several weeks following adequate thyroidectomy the administration of desiccated thyroid and iodine should be continued until after delivery in an effort to avoid abortion secondary to hypothyroidism.[1]

There should be individualization in the choice of therapeutic procedures in dealing with pregnant patients with thyrotoxicosis. The long-term use of antithyroid drugs intended as the only therapy of hyperthyroidism in pregnancy seems inappropriate in most cases, because there is evidence that the duration of the drug therapy has a direct relationship to the incidence of fetal abnormalities.[17] Under certain circumstances, however, antithyroid drugs alone may be the treatment of choice for the duration of the pregnancy. This is true of patients with such complications as severe heart disease and postoperative recurrent hyperthyroidism in whom operation should be avoided if possible. Following delivery patients who are not suitable candidates for thyroidectomy either can be continued on an antithyroid drug in an effort to induce a permanent remission, or they can have their problem more definitively settled by the administration of therapeutic doses of radioactive iodine. It should be borne in mind, however, that I^{131} and antithyroid drugs are excreted in breast milk in such concentrations as to be potentially harmful to the nursing infant's thyroid.[23, 26] If the thyrotoxicosis cannot be controlled early enough to permit operation during the first six months of pregnancy, or when hyperthyroidism first appears in the last trimester, thyroidectomy should probably be deferred until after delivery.

As to the role of therapeutic abortion in the management of thyrotoxicosis complicating pregnancy, Means,[20] over 20 years ago, expressed the opinion that "It is the

* Case previously reported by Krementz *et al.*[19]

thyrotoxicosis, not the pregnancy, which should be interrupted." Now that it is possible with the use of the antithyroid drugs to control completely the severest degree of hyperthyroidism, therapeutic abortion would appear to be not only unnecessary but actually contraindicated except under the most unusual circumstances. The abortion does not cure the hyperthyroidism, it may precipitate a thyroid crisis in the woman with uncontrolled thyrotoxicosis, and in the patient who has been rendered euthyroid its performance is probably more risky than a properly executed thyroidectomy.

Hyperthyroidism and pregnancy are so infrequently associated that the experience of most clinics is limited to relatively few cases. Perhaps this partially explains the wide discrepancy in reports concerning the incidence of fetal and maternal complications when the pregnant patient has thyrotoxicosis. While it would be wrong to infer that with the advent of modern therapy the answers to these questions became of only academic interest, it does seem reasonable to suggest that it is now possible to control hyperthyroidism with such promptness and safety that these considerations have become of less practical clinical importance.

Summary

At the Charity Hospital in New Orleans approximately one pregnancy in 5,000 is complicated by hyperthyroidism. This is a much lower incidence than the average figure of one in 500 recorded in the literature.

During pregnancy, treatment of the hyperthyroidism consisted of preoperative preparation with antithyroid drugs and/or iodine followed by subtotal thyroidectomy in eight patients; administration of antithyroid drugs alone in 20 patients; and the use of iodine alone in two instances. There were no maternal deaths.

The results of 42 pregnancies in 30 thyrotoxic women were: 29 full-term normal deliveries with 29 infants, three of which had goiters; six spontaneous abortions; four premature births of healthy infants; and three term stillbirths. This represents a fetal loss of 24 per cent.

The relative rarity with which hyperthyroidism is associated with pregnancy is partially responsible for the diversity of opinion as to the effect of pregnancy on the etiology and course of hyperthyroidism, the effect of thyrotoxicosis on pregnancy and the fetus, and the appropriate treatment of hyperthyroidism under these circumstances. An analysis of the Charity Hospital experience in this connection, and a review of many relatively small reported series failed to provide unequivocal answers to these controversial questions. We believe that most surgeons and obstetricians would regard as reasonable the following suggestions:

1. Pregnancy does not appear to be a major factor in the initiation of hyperthyroidism; and in most instances it does not influence the course of the disease or its response to treatment.

2. Early recognition and prompt control of thyrotoxicosis will reduce whatever influence it may have on the incidence of such complications of pregnancy as abortion, stillbirth, premature delivery and toxemia. Hyperthyroidism *per se* probably does not exert a deleterious effect upon the fetus.

3. Administration of radioactive iodine is contraindicated during pregnancy because it crosses the placental barrier and may destroy the fetal thyroid.

4. The thiourea derivatives also traverse the placenta and are capable of exerting harmful effects upon the fetal thyroid; and whenever possible their long-term use should be avoided.

5. Most pregnant patients with hyperthyroidism are best treated by subtotal thyroidectomy after rapid preparation with antithyroid drugs and/or iodine. Thyroidectomy can be performed during pregnancy without undue risk to mother or fetus.

6. Hypothyroidism is a threat to both mother and fetus, and its induction by ex-

cessive dosage of antithyroid drugs is to be avoided. During pregnancy it is especially important to anticipate and appropriately treat the transient hypothyroidism which often follows adequate thyroidectomy.

Bibliography

1. Bell, G. O.: Hyperthyroidism, Pregnancy and Thiouracil Drugs. J. A. M. A., **144**:1243, 1950.
2. Brandes, R. W.: Pregnancy Complicated by Thyroid Disease Amenable to Surgical Treatment: A Clinical and Pathologic Study. Thesis, Univ. of Minn. Grad. Sch., 1948.
3. Chapman, E. M., G. W. Corner, Jr., D. Robinson and R. D. Evans: Collection of Radioactive Iodine by Human Fetal Thyroid. J. Clin. Endocr., **8**:717, 1948.
4. Clute, H. M. and D. H. Daniels: Hyperthyroidism and Pregnancy. Am. J. M. Sc., **179**: 477, 1930.
5. Dailey, M. E. and R. C. Benson: Hyperthyroidism in Pregnancy. Surg., Gynec. & Obst., **94**:103, 1952.
6. Fahrni, G. S.: Pregnancy Complicating Hyperthyroidism and Following Thyroidectomy. Canad. M. Ass. J., **23**:645, 1930.
7. Falls, F. H.: Hyperthyroidism Complicating Pregnancy. Am. J. Obst., **17**:536, 1929.
8. Freiesleben, E. and K. Kjerulf-Jensen: The Effect of Thiouracil Derivatives on Fetuses and Infants. J. Clin. Endocr., **7**:47, 1947.
9. Gardiner-Hill, H.: Pregnancy Complicating Simple Goiter and Graves' Disease. Lancet, **1**:120, 1929.
10. Goldsmith, E. D., A. S. Gordon and H. A. Charipper: An Analysis of the Effects of Continued Thiourea Treatment in Pregnancy and on the Development of the Offspring in the Rat. Am. J. Obst. & Gynec., **49**:197, 1945.
11. Hone, G. M. and I. Magarey: Cretinism Associated with Methyl Thiouracil Therapy. Med. J. Australia, **2**:524, 1948.
12. Hughes, A. M.: Cretinism in Rats Induced by Thiouracil. Endocrinology, **34**:69, 1944.
13. Hodges, R. E., T. C. Evans, J. T. Bradbury and W. C. Keettel: The Accumulation of I^{131} by Human Fetal Thyroids. J. Clin. Endocr., **15**:661, 1955.
14. Javert, C. T.: Hyperthyroidism in Pregnancy. Am. J. Obst., **39**:954, 1940.
15. Jondahl, W. H., E. A. Banner and L. P. Howell: Management of Pregnancy Complicated by Toxic Goiter. Report of Case. Proc. Staff Meet. Mayo Clinic, **24**:358, 1949.
16. Kauffman, G., V. Hurst and C. W. Turner: Histological Effect of Thiouracil on the Fetal Thyroid of the Mouse. Endocrinology, **43**: 187, 1948.
17. Keynes, G.: Obstetrics and Gynecology in Relation to Thyrotoxicosis and Myasthenia Gravis. J. Obst. & Gynec. Brit. Emp., **59**:173, 1952.
18. Kibel, I.: Hyperthyroidism and Pregnancy. Am. J. Obst., **48**:553, 1944.
19. Krementz, E. T., R. G. Hooper and R. L. Kempson: The Effect on the Rabbit Fetus of the Maternal Administration of Propylthiouracil. Surgery, **41**:619, 1957.
20. Means, J. H.: Thyroid and Its Diseases. First Edition. Philadelphia: J. B. Lippincott Co., 1937.
21. Mussey, R. D., S. F. Haines and E. Ward: Hyperthyroidism and Pregnancy. Am. J. Obst., **55**:609, 1948.
22. Peterson, R. R. and W. C. Young: The Problem of Placental Permeability for Thyrotropin, Propylthiouracil and Thyroxine in Guinea Pig. Endocrinology, **50**:218, 1952.
23. Russell, K. P., H. Rose and P. Starr: The Effects of Radioactive Iodine on Maternal and Fetal Thyroid Function During Pregnancy. Surg., Gynec. & Obst., **104**:560, 1957.
24. Russell, K. P.: Evaluation of Thyroid Function During Pregnancy. Postgrad. Med., **22**:578, 1957.
25. Valensi, G.: Tunisie Med., **36**:39, 1958. Cited in Foreign Letters, J. A. M. A., **167**:1028, 1958.
26. Williams, R. H., G. A. Kay and B. J. Jandorf: Thiouracil; Its Absorption, Distribution, and Excretion. J. Clin. Invest., **23**:613, 1944.

Discussion

Dr. James D. Hardy: When we received the program we reviewed our cases of hyperthyroidism in pregnancy. There had been six cases over the period of three years. Of these, five had had their disease prior to pregnancy. They had come in at various stages of pregnancy. Two had been operated upon, one in the fifth month and one in the sixth month; neither aborted. One patient aborted two days following admission, before the antithyroid drugs had had time to take effect.

I talked with Dr. Michael Newton, Professor of Obstetrics and Gynecology, and with Dr. Herbert G. Langford, Director of the Endocrine Clinic, and found that we were in substantial agreement regarding the following points: If the patient were seen early in pregnancy, the hyperthyroidism would