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## Thyrotoxicosis during pregnancy

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THYROTOXICOSIS DURING PREGNANCY

by

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Nebraska College of Medicine in Partial  
Fulfillment of the Requirements  
for the Degree of Doctor  
of Medicine

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## Introduction

There is no complication of pregnancy about which more is known and yet presents so much difference of opinion as in the subject of hyperthyroidism during pregnancy. The pathological physiology as well as etiology of the toxemias of pregnancy are things which everyone seems to pass up with the three words, "We don't know", in the final clause of the discussion. The treatment is to a certain degree favorable. In thyrotoxicosis during pregnancy, the etiology and pathology as well as the treatment have been worked out to the point where nothing is left for speculation and theorizing, and yet the ideas of almost every writer differ in major questions of the problem.

This discussion is an effort to present the ideas of the authorities on the subject. As will be apparent later, this is difficult to do since these ideas are so completely different. The subject of hypothyroidism has received only little space and there has been an effort to omit it in the discussion in so far as possible. However, references are made to the condition more especially in the discussion of the physiology of the thyroid gland. The

reason for this is that most major physiological observations were made under experimental hypo- and hyperthyroidism.

The thyroid gland in its relationship to the other endocrine glands is a subject within itself. Only concrete evidences of experimental nature which seem to indicate what actually happens in the thyroid gland when pregnancy occurs has been presented. The remainder I have not stressed because there is so much theorizing which I have attempted to eliminate from what I have tried to make a practical discussion of my subject.

Resume of the Anatomy, Physiology, and Pathology of  
the Thyroid Gland

The thyroid gland consists of two lobes joined together across the trachea by a narrow transverse portion called the isthmus. It extends from the junction of the middle with the lower third of the thyroid cartilage downwards to the level of the fifth or the sixth tracheal ring. It normally weighs one ounce in the male and slightly more than this in the female. Emmert (15) points out that the isthmus at times is absent and that there is at times a third lobe called the pyramid which arises from the isthmus or left lobe and extends upward as far as the hyoid bone. It may be entirely separated from the gland and be divided into several parts. The gland is enveloped in a connective tissue capsule which is thin anteriorly and increases in thickness as it passes around toward the posterior surface.

Mayo and Plummer (34), in a very complete discussion of the anatomy, physiology, and pathology of the thyroid gland, call our attention to the fact that the gland is richly supplied with blood. The superior thyroid arteries enter each superior pole and anastomose freely

with the inferior thyroids which enter the lower pole of each lobe. At times the thyroid ima, a small vessel arising from either the innominate or the arch of the aorta, ascends the anterior surface of the trachea and supplies the lower portion of the gland. The veins are numerous and large and follow the main arteries, except for the middle thyroidal veins which leave the gland from either side and empty into the innominate veins.

Much more was known in the past of the anatomy of the thyroid gland than of its function. Crotti (7) in his very interesting discussion of the history of the thyroid gland enumerates several most fascinating theories as to the physiology of the gland. He shows how the physiologists of antiquity considered the thyroid as a cosmetic organ whose function it was to produce a nice soft roundness of the neck. Others considered it as a mechanical support to the larynx and thought that it protected this organ from the cold. Another group of men considered the gland as one of external secretion, its secretion being poured into the region of the vocal cords and furnishing the necessary lubrication to these cords. Still others considered a communication with the esophagus and marked the excretory canal as being at the foramen cecum.

As new and more scientific observations were being made all along, the extreme vascularity of the thyroid gland was noticed. This set off a new line of thought. The gland was considered as a mechanical regulatory organ of the blood stream, its engorgement resulting in pressure on the carotid vessels with a cerebral anemia, a sort of safety valve for the cerebral circulation. Along this same time, one observer considered the gland as the organ of sleep by the mechanism brought out above and cerebral anemia resulting in unconsciousness.

At the present time physiological studies are made under conditions of experimental hyperthyroidism by feeding thyroid substance and by experimental hypothyroidism as by removal of the thyroid gland in animals. It was along these lines that the observations of Kocher and Reverdin were directed.

Probably the first true scientific observation made, according to Ward (45) (46), was that of Parry in 1786. Parry observed hyperthyroidism but his observations were not accepted and the syndrome was as much unexplained as previously. In 1835 Graves made his epoch making discoveries and the subjects of thyroid physiology and pathological physiology were much advanced.



In the beginning it had been observed that if thyroid substance is given to animals or humans a certain train of toxic symptoms occur. This complex, made up of exophthalmas, tremor, loss of weight, trachecardia, headache, polyphagia, vertigo, mental excitation, nausea, vomiting, polyuria, albuminuria, and glycosuria, was called acute thyroidism and occurs as we see it today in the hyperthyroid state.

Grotti (7) sums up the physiological activities of the thyroid gland under seven headings:

1. Heat regulation. Experiments in which thyroid substance was fed to hibernating animals revealed an increased temperature and activity.
2. Action on the cardiovascular system. When thyroid extract was given by vein there was a lowering of the blood pressure and a peripheral vasodilatation. There are numerous theories as to the mechanism of this phenomenon all of which have their strenuous advocates and opposers.
3. Action on the blood. After complete thyroidectomy, an anemia resulted which returned to the normal state after thyroid feeding. Is it hemopoietic?
4. Action on nutrition. In the symptom complex of acute thyroidism the metabolism is whipped up, the oxidat-

ive processes are more rapid in each cell in the body, more waste products are being formed and more food utilized.

5. Action on the osseous system. Following total thyroidectomy, trophic disturbances were observed in the osseous system. It was noticed that the younger the animal the more pronounced these trophic changes.

6. Action on the nervous system. A severe neuritis was demonstrated after complete thyroidectomy in the laboratory animal which followed in most cases by a parenchymatous encephalitis. In the hyperthyroid state it is of common observation that the patient has an hyperactive nervous system with tendency to emotional instability and pronounced tremor. No microscopic changes in the nerves have ever been reported in hyperthyroidism however.

7. Modification of the urine. In hyperthyroidism there is an increase in the urine output with a high phosphate. In hypothyroidism there may be a febrile albuminuria.

Much experimental work has been done in the past few years in an attempt to place the thyroid in the physiological "endocrine chain". The work of Knaus (25) (26) and others should be mentioned.

Knaus (25) injected virginal rats from two to four weeks with extracts from the corpus luteum. He reports a thyroid hypertrophy with an increase in the amount of the colloid in these goiters. From his observations he concludes that the corpus luteum causes an inhibition of the output of thyroid secretion. However, he found that these animals gained weight which speaks against hyperthyroidism. The analogy of the findings of Knaus with the changes in the thyroid during pregnancy is very close as will be pointed out later.

Loeb and Bassett (23) removed the anterior pituitary of rats and observed an atrophy of the thyroid gland. A standard pituitary extract (Armours) was fed and the thyroid failed to regenerate. These workers then prepared both acid and alkaline extracts of the dried anterior pituitary of cattle and promptly got an hypertrophy of the thyroid gland which previously had been partially removed. This observation was also made by Bothe (5) who, besides demonstrating glandular hypertrophy following pituitary injections, demonstrated an increased secretion of the gland as measured in the blood.

Ansilmino and Hoffman (1) (2) demonstrated the presence of thyroxin (or a substance having the characteristics of thyroxin) in the blood of normal men and women

and showed quite conclusively that there was a marked increase during pregnancy which reached its highest level toward the end of pregnancy and dropped to normal after delivery. These men also demonstrated an increased carbon dioxide output in rats that had had daily injections of pregnant human serum with no demonstrable increase in the carbon dioxide output when the injections were done with normal human serum. Clute and Daniels (8) bring out the importance of the thyroid-ovarian interrelationship. Their conclusions were that the more active the thyroid, the less active the ovary and this is borne out in a practical way when the extremely low incidence of hyperthyroidism associated with pregnancy is brought out.

Knaus (26) made intravenous injections of 6.02 mg. of epinephrine in thirty five multiparas and primiparas in the later half of pregnancy, immediately followed by subcutaneous injections of 0.8 to one mg. of epinephrine. From the responses that he got in this experimental work seem to indicate that epinephrine causes a decrease in the thyroid secretion and that pregnancy edema may be adequately combated by the use of thyroid extract. He concludes that there is some hook up between the thyroid secretion and the toxemias of pregnancy. The work of Fruhinholz (19) seems to bear out this conclusion since

He observed four cases of myxoedema and pregnancy all of which presented some findings of pregnancy toxemia.

Marine and his coworkers (31) (32), in an experimental study on eighteen pregnant rats showed that after iodine had been fed that there was no change in the heat production in eleven, an increase in two, and a decrease in five. At term pathological studies of the gland showed no apparent change or difference. However, Steward and Meene (42) in a study of pregnant rabbits demonstrated a smaller increase in basal metabolic rate (3.6%--2.9%) where physiological doses of iodine were given than in those in which no iodine had been given (39.2%--45%).

With the accumulation of experimental material which has been brought out in the past few years, there have been no specific conclusions drawn as to the exact role the thyroid plays in relationship to the other endocrine glands or the specific effect iodine plays in thyroid metabolism other than to say that it seems to render some unknown element usable and to reduce the toxicity of a toxic thyroid gland.

Pathologically, Boyd (6) points out that the thyroid gland is peculiar in that it is only seldom affected by

the four great causes of disease elsewhere in the body namely inflammation, tuberculosis, syphilis, and malignant disease. However, it commonly presents a condition of enlargement, diffuse or localized, which may or may not be accompanied by symptoms of grave disturbance of general metabolism. Numerous descriptive terms have been used in the past to indicate certain processes which have taken place in the gland. Such terms as parenchymatous goiter, hyperplastic goiter, non hyperplastic goiter, cystic goiter, etc, have resulted in much confusion in pathological studies. At present however, with the increased understanding in morbid processes in the gland, these states are, as pointed out by Virchow (43), only part of a general pathological entity.

The pathogenesis of goiter is well given by Boyd (6). He states that "the thyroid, as already indicated, may be played upon by a variety of stimulæ, to which it reacts by hyperplasia, either of the adult or of the embryonic cells, It does not follow therefore, that it is necessary to look for one constant and invariable cause of goiter. In some cases it may be due to bacterial infection which possibly uses up the iodine necessary for the normal functioning of the gland in others it may be due to

deficiency of iodine in the food, in others to physiological stimulæ such as puberty, menstruation, and pregnancy, in yet others to severe psychic shock as for instance in the cases of exophthalmic goiter which developed suddenly upon bombardment of towns during the world war. Even these cases may be merely demands for a greater iodine supply than is available. The stimulus is followed by hyperplasia. When the stimulus is withdrawn the hyperplasia ceases, and the gland returns to normal. Such for instance, is the thyroid enlargement of menstruation and pregnancy. Everything depends upon how far the hyperplasia has gone. If it is very slight the gland may return to normal. If it has proceeded further the best that can be done is a return to a resting stage in which the gland is permanently damaged, a condition of colloid goiter. If the stimulus is continued, the hyperplasia progresses indefinitely".

With a fundamental understanding of the physiological and pathological processes as outlined above, comes an understanding of the complicated picture that is presented in the hyperthyroid state.

The clinical classifications of goiter are as complicated as the pathological discussions. For pract-

ical considerations the classification suggested by the Committee on Classification appointed by the American Medical Association for the Study of Goiter is complete. It is as follows:

Type 1. Non Toxic Diffuse Goiter

Type 2. Toxic Diffuse Goiter

Type 3. Non Toxic Nodular Goiter

Type 4. Toxic Nodular Goiter

The older writers use the older classification of thyroid disturbances, which is as follows:

Type 1. Colloid Goiter

Type 2. Non Toxic Adenomatous Goiter

Type 3. Toxic Adenomatous Goiter

Type 4. Exophthalmic Goiter

This classification, though less convenient from a clinical standpoint, will be used throughout this discussion in order that misinterpretation of the literature will be avoided.



## The Thyrotoxic State--Exophthalmic Goiter and Toxic Adenoma

The clinical picture of these two conditions may best be understood by quoting the description of Boothby (4). He states that "exophthalmic goiter may be described as a constitutional disease, apparently due to an excessive, probably abnormal secretion of an enlarged thyroid gland showing diffuse parenchymatous hypertrophy; it is characterized by a high basal metabolic rate with the resulting manifestations, with a peculiar nervous syndrome, and with a tendency toward the gastrointestinal crisis of vomiting and diarrhea. In contrast, the symptoms of adenomatous goiter are those essentially due to a prolonged elevation of the basal metabolic rate caused by the presence in the tissues of an excess of a normal thyroid secretion; exophthalmos does not occur and the symptoms are not associated with typical diffuse parenchymatous hypertrophy but with the occurrence of adenomatous tissue of the thyroid gland. At least one third of all exophthalmic goiters have superimposed adenomas!"

The clinical picture of an exophthalmic goiter is quite variable. Early there may be a sense of fatigue with nervous excitability and loss of weight. The

appetite may be excessive and in spite of the increasing fatigue, there may be an inward drive urging the patient on to purposeless activity. The skin is usually warm and flushed and the patient perspires easily.

Mayo and Plummer (34) list the symptoms of exophthalmic goiter in order of their importance.

1. Palpitation. The cardiac rate may reach 160 and is persistent during sleep. Auricular fibrillation is common.
2. Warm damp skin. With flushing of the face and generalized superficial vasodilatation.
3. Tremor. The patient suffers from a constant intention tremor which seems to get worse as time goes on.
4. Eye changes, consisting of:
  - a. Exophthalmos with a more or less fixed staring expression, the eyes are unusually bright.
  - b. Infrequent blinking--Stellwags sign.
  - c. Weakness on convergence--Moebius sign.
  - d. Lid lag--On looking downward the upper lid follows slowly or not at all. von Graefe's sign.
5. Nervous manifestations. There may be nervous instability with unexpected losses of temper. True psychosis occasionally occurs.

6. Tumor in the neck. This finding may be marked or entirely absent. A "bruit de diadle" may be demonstrated over the gland.

The findings of a toxic adenoma are much the same as those listed above with a few exceptions. This condition, as brought out by Wallace (44), occurs at a later time in life and thus the relative infrequency of adenoma in pregnancy. Also, the eye changes listed above are, according to Du Bois (14), seldom a part of the clinical picture. He brings out an important fact when he states that "the constitutional symptoms of toxemia from adenoma often come without apparent cause but is sometimes initiated by the administration of iodine and once started, continues even after the iodine has been withdrawn".

## The Relation of the Thyroid Gland to Pregnancy

The profound changes which result in the female from pregnancy have been recorded by almost all writers. What influence the thyroid gland has in bringing about these changes is questionable, but such authorities as Falls (17), Mussey and Plummer (35), Wallace (44), Yoakam (48), Bothe (5), Davis (11) (12), and Beck (3) all agree that the early physical manifestations of pregnancy may be placed in general on a basis of change in the endocrine interrelationships and more specifically on the basis of an increased thyroid secretion. The symptoms associated with early pregnancy of nausea, vomiting, nervousness, increased excitability, and tachecardia, associated with an increase in size of the thyroid gland are commonly seen. At times there may even be slight exophthalmos. This is especially brought out by Falls (17).

Yoakam (48), who has made extensive studies in regions of endemic goiter, comes to the conclusion that the demands on the thyroid gland are increased during pregnancy and an hypertrophy of that organ results. He points out that this is especially true if the iodine intake is impaired as it was where his studies were made.

However, later in his article he states that "the so called physiological enlargement of the thyroid gland is in reality a pathologic hyperplasia which may be prevented by the administration of sufficient iodine in the diet during pregnancy".

Marine (30) states that there is always some decrease in the iodine content of the thyroid gland during pregnancy showing the necessity of iodine administration during gestation. He also brings out the fact that in areas of endemic goiter the incidence of low iodine content in the thyroids of babies born of goiterous mothers and strongly urges the use of iodine to prevent the maternal hypertrophy and to increase the iodine content of the fetal thyroid gland so preventing congenital goiter.

Soule (41) made studies of the thyroid gland in normal pregnancy and demonstrated that the glycogen level in the body was decreased with any increase in the activity of the thyroid gland. He also demonstrated a higher concentration of thyroxin in the maternal blood than in the blood of the fetus.

The findings of Knäus (25) (26) seem to indicate, as was brought out above, that there is some connection between the corpus luteum and thyroid hypertrophy. It is

known that the corpus luteum continues its hypertrophy and internal secretory powers well into pregnancy as the corpus luteum vera. The work of Knaus seems to indicate that this new gland of internal secretion causes the thyroid hypertrophy so commonly seen during pregnancy, since he got thyroid hypertrophy in virginal rats with injections of corpus luteum substance.

Falls (17) sums up the endocrine state by saying that "it is not easy to explain what actually happens in these but we believe that there is a stimulation of the sympathetic nervous system and all the glands of internal secretion. As a result there is a readjustment of these glands relationship to each other and to the organism as a whole. When the readjustment occurs in the right direction, the goiter symptoms do not appear or are improved but when it occurs in the reverse direction the toxic phenomena are aggravated".

There has been much work of late in an attempt to determine the exact state of the metabolic processes in the body of the pregnant woman. Plass and Yoakam (37) conclude that the increased body activity as manifested by an increased basal metabolic rate is due to the increased protoplasmic mass alone and not to some inherent.

mysterious body process of unknown nature. These workers prove their statement by subtracting the calculated heat production of the fetus from the total heat production of the pregnant woman, leaving the metabolic rate of the latter unaffected by gestation. Immediately after delivery the basal metabolic studies of the woman were found to be normal and the extra load as manifested by the basal metabolic studies before labor were found to correspond almost exactly with the measured metabolic rates of the newborn. However, Soule (41) concludes that the increased metabolism is not due to the fetus alone but to some change in the mother since, as was stated above, a higher concentration of the thyroxin was demonstrated by him in the maternal blood than in the blood of the fetus.

### Thyrotoxicosis During Pregnancy

In a study of toxic thyroid during pregnancy, one is immediately impressed by the scarcity of the condition. In the various clinics throughout this country and Europe the incidence is quite variable as one would expect with the existence of the so-called "goiter belts". Another thing of interest is the dearth of material on the subject. The literature from 1921 to 1931 in the *Index Medicus* for the ten year period contains only sixteen articles in all languages dealing or bearing upon the subject. Some of these were only case reports. Since then there has been some excellent records of observations in the larger clinics in the United States and Europe. The work of the Japanese should be brought out on this subject but unfortunately none of them can be mentioned here because of unfamiliarity with the language and the scarcity of abstracts in the English and German languages.

It has been observed for many years that pregnancy has an effect on the activity of both the normal thyroid gland and the toxic gland. Observers have noticed that this effect may be an increased activity of the normal or pathological gland, that it may be a decrease, or that



there may be no change at all. One thing is certain. With the activity of the thyroid increased, the activity of the ovary is reduced. This is especially brought out by Lahey (27), Gardiner-Hill (21), Davis (12), Clute and Daniels (8), Plass and Yoakam (37), and Beck (3). This explains the relative sterility which is so often a part of the hyperthyroid state, as manifested by the low incidence which will be brought out below.

Gardiner-Hill (21) concludes from his studies that there is no evidence to show that pregnancy makes the case of hyperthyroidism worse. On the contrary, some of them are made distinctly better by pregnancy. Seitz (40) shows that pregnancy did not affect the hyperthyroidism in 40% of his cases, but in 60% the toxic symptoms were made much worse. Mussey, Plummer and Boothby (36) did not find that pregnancy made the case of toxic thyroid any more difficult to handle or influenced it in any way. Clute and Daniels (8) state that they have seen nothing occur in any woman with hyperthyroidism and pregnancy which did not occur in the non pregnant thyroid cases of that type. They state that multiple stage thyroidectomy has been just as necessary in pregnant as in non pregnant women but no more so. However, these authorities believe

that pregnancy during hyperthyroidism is an added load for the patient to endure whether it does or does not affect the degree of toxicity which is present. Pregnancy increases the patients muscular work and adds to the metabolic requirements. These men state that it is their daily experience to note that thyrotoxic patients cannot tolerate the added loads and they feel certain from this standpoint, pregnancy is a serious burden in all severe thyroid intoxications. Beck (3) states that patients with Graves disease whose thyroids have already been functioning excessively before conception occurred, improve subjectively during pregnancy. This he attributes to the absence of the menstrual cycle which, in the non pregnant state, is one of the main causes of increased body metabolism.

Wallace (44) studied 11,571 cases of pregnancy from the thyroid angle and concluded that there was no evidence to show that pregnancy was in any way responsible for exciting a thyrotoxicosis that made operation necessary later and in those where pregnancy occurred following thyroidectomy, no recurrence of symptoms was caused by it. In his studies, Davis (11) (12) found that 41% of 520 pregnant women had thyroid hypertrophy. The condition

was usually transient but eight of this group returned with toxic symptoms after delivery. Flass and Yoakam (37) conclude through extensive basal metabolic studies that there is an increase in the thyroid activity in nearly all pregnant women. They show a gradual increase to about an average of 15% at term with a rapid fall to normal in the first few days post partum. A greater rise and a slower fall to normal is indicative of pathological change incident to pregnancy.

Hinton (23) (24) states that 40% to 90% of all women have hypertrophy in pregnancy, and Frazier and Ulrich (20) show a consistent increase of 15% in the basal metabolic rate in all women.

From what has gone before, we see that the course of a mildly toxic case may be quite variable. She may be distinctly better, she may be worse, or she may show no change. This is true of the more toxic cases and we see that this is distinctly not in accord with the ideas of Gellhorn (22), who states that an exophthalmic goiter, though only moderately toxic, should not marry, if she marries she should not become pregnant, if she becomes pregnant she should be aborted.

As to the incidence of true toxic goiter during preg-

nancy, the figures of the larger clinics may be mentioned. Lahey (27) in Boston, in 3,678 patients he operated for toxic goiter, found that 15 were pregnant, or an incidence of 0.41%. Mussey and Plummer (35) at the Mayo clinic, found 42 cases in 7,228 pregnancies, or an incidence of 0.6%. Yoakam (48) in Detroit, (in a goiter belt) found that 3.7% of pregnant women had coexistent thyroid disturbance. Markoe (33) in New York, found eight cases in 100,000 pregnancies in the New York Lying In. Wallace (44) in Brooklyn, found in ten years from 1921 to 1931, nine cases out of 11,571 pregnancies. The above cases as recorded by these men are toxic cases and there was no doubt as to whether the thyroid was toxic or whether it was a "normal hypertrophy of pregnancy" that was mentioned.

Seitz (40) in Germany records 112 toxic cases. Of these, 15% progressed to an alarming degree. In this group there were seven deaths, five therapeutic abortions, premature labor in eleven, thyroidectomy was performed in seven, and three had premature births. His results do not compare with those in the United States as far as incidence is concerned. Frazier and Ulrich (20) give an incidence of 3.2% of women in whom thyroidectomy had been done, later developed thyrotoxicosis during pregnancy.

In drawing a conclusion from what has gone before, one is immediately at a loss to say anything specific. Two facts are prominent. First, the incidence of thyrotoxicosis during pregnancy varies in direct proportion to the incidence of uncomplicated goiter in that area. Second, the effect of pregnancy on an already toxic gland is variable and can be accurately determined only as pregnancy advances. This second statement shows just how difficult it is to follow the advice of Mussey (36) who says that the case in question must be studied very carefully and an attempt made to foresee what is going to happen and direct treatment along those lines.

## Clinical Considerations of Thyroid Toxemia in Pregnancy

Following are two case histories representing thyroid toxemia during pregnancy. The first case represents the more common type seen almost daily. The second case is one of the more acute and serious type which requires expert care in its management. The similarity of these two cases is striking and seems to be only a matter of degree of toxicity.

### Case I

Mrs H.S., married housewife, age 20, primipara, had her last normal menstrual period on April 19, 1934. She had been perfectly well except for some nervousness, occasional loss of temper over trivial matters, and slight fullness in the neck since puberty. Her speech had always been rapid and thick with distinct lack of enunciation when she became the least bit excited. This condition had been present since puberty also.

She had had the usual childhood diseases and for the past year had been receiving injections of an autogenous vaccine for a mild form of pyoderma which had been quite persistent during this time. Other than this her past history was negative.

During the months of April, May and June, 1934 her condition was not much changed except for the normal changes which occur during the first trimester of pregnancy. About the fourth month she noticed the development of furuncles about the forearms and arms which went on to suppuration and were adequately drained. At this time she became more

nervous, had a slight tremor, trachecardia and her hands were damp and warm. Her face was moderately flushed and her appetite was excessive. The thyroid gland increased in size to the point where the borders of the sternocleidomastoid muscles no longer could be seen. This was diffuse hyperplasia and the gland was soft. She had never been troubled with nausea or vomiting and her blood pressure was consistantly below 130 systolic and 90 diostolic. Her urine was negative for albumin and her blood picture was essentially normal.

The course on through pregnancy was uneventful. During the last trimester her condition remained as outlined above. She had a second attack of the skin infection at the seventh month which cleared up and gave her no further trouble.

She went into labor about 10 A.M. on February 10th, 1935 and delivered a normal female child weighing eight pounds and thirteen ounces at 8:30 P.M. A second degree laceration was repaired and she returned home on the fourteenth day in fair physical condition.

At the time of this writing no deffinate statement can be made as to this girls present condition. She is at the present time not much better than she was before delivery. She is still rather nervous and irritable but the condition has been accentuated by some family troubles which have caused her no little amount of concern and worry. She has however, a mild degree of subinvolution as a residual with a persistant vaginal discharge which has required rather vigorous treatment.

This type of case is seen most frequently by the obstetrician. It represents a type stressed by Daly and Strouse (9) in their paper. These men stress the importance of the symptoms of irritability, nervousness,

and emotionalism seen very frequently during pregnancy and place them clearly upon a thyroid basis. It seems to indicate that pregnancy makes an already mildly toxic thyroid gland worse and is distinctly not in accord with the ideas of Clute and Daniels (8) who consider any increase in toxicity of the thyroid gland as due to an increase in the protoplasmic mass alone. There seems to be an added factor here, possibly infection, but of course no conclusion can be drawn from the facts presented in a single case. Bothe (5) also brings out the importance of this type of case in his discussion. He points out the difficulty sometimes encountered in making the diagnosis of hyperthyroidism during pregnancy. Robinson (39) observed subinvolution very frequently in these cases and along with the symptom of tendency to bleed noted by Luker (29) in thyroid cases constitute two symptoms not mentioned by the majority of writers.

#### Case II

Mrs A.J., 32 years of age, entered the University Hospital obstetrical service on January 9, 1934, complaining of:

1. Tumor in the abdomen of four months duration.
2. Tremor, tachecardia, nervousness, tumor in the neck and loss of weight of eight years duration.



She had always been perfectly well until eight years ago when she developed an enlargement in the neck which was diagnosed as goiter. With the onset of her pregnancy one year later, she became very irritable, restless, and easily fatigued. She was disturbed greatly with palpitation, sensitiveness to heat, and became quite dyspnoeic with slight exertion. Her appetite became excessive. All the symptoms progressed and at the termination of the pregnancy six years ago she was operated upon. Two months later the patient returned to her surgeon complaining of persistence of the above symptoms. Reoperation was advised but refused and in compromise, the neck was irradiated with radium. There was marked recession of symptoms and much improvement in her general condition.

Since the onset of her present pregnancy seven months ago there has been a gradual but definite increase in the toxicity of her goiter. During the past four months her ankles have become progressively more edematous and one month before admission her physician observed a blood pressure of 180 mm of mercury, and that the urine contained albumin. A week later the systolic pressure had gone to 210.

The past history was essentially negative.

Physical examination upon admission showed the patient to be very nervous and restless with a damp warm skin. There was moderate exophthalmos with associated eye signs and a fixed anxious stare. Her face was markedly flushed. The nose and throat examinations were negative, her teeth were in good repair. At the base of the neck there was a narrow scar of the previous operation and the skin of the area showed evidences of atrophic changes from excessive radiation. On each side of the trachea there was a mass about the size of a lemon of unusual consistency, both were hard but elastic, slightly nodular and fixed to the surrounding tissue. No isthmus was palpated.

The lungs were clear throughout. The heart was moderately enlarged and the sounds were loud and snappy with an accentuation of the pulmonic second sound. There was a loud systolic murmur throughout the precordium. The blood pressure was 200 systolic and 100 diastolic.

The abdomen was negative except for a seven months pregnancy. The fetal position was left occiput anterior and the fetal heart sounds were heard in the lower left quadrant and recorded as 142 beats per minute. Vaginal examination revealed only the signs of pregnancy.

There was moderate pitting edema of both ankles, a marked fine rapid tremor of the fingers and hyperactive reflexes.

The laboratory revealed a three plus albumin in the urine, an erythrocyte count of 4,320,000 with 80% haemoglobin, a white count of 9,100 and a normal differential count. Extensive blood chemistry was essentially negative, and the quantitative albumin measured 3 grams in 24 hours. The basal metabolic rate was plus 78. Roentgenographic studies of the chest showed moderate cardiac enlargement, some passive congestion of both lung fields, no prolongation of a substernal thyroid, and no evidence of an enlarged thymus gland. The electrocardiogram presented evidence of trachecardia and left axis deviation.

From the data above, the diagnosis was made of :

1. Persistent hyperthyroidism.
2. Pregnancy of seven months duration.
3. Nephrosis and possible pre-eclamptic toxemia.

She was treated conservatively with absolute bed rest, sedation, a low protein diet which was salt free, small doses of calcium lactate and potassium citrate, several purges with magnesium sulphate, and repeated short courses of digitalis and Lugol's solution. The above treatment gave no noticeable change in her condition.

On February 12, 1934, a little over a month after her admission, the patient became alarmingly sick with evidences of thyroid crisis. Her temperature rose to 103 degrees, her pulse to 160 and her blood pressure to 220 systolic and 120 diastolic. Her urine was loaded with albumin and showed numerous granular casts. Her condition became progressively more critical until the pregnancy terminated spontaneously on the following day. Immediately she began to improve and within 48 hours the temperature had returned to normal, her pulse rate to 120 per minute and her blood pressure to 160 systolic and 100 diastolic. One week after delivery the basal metabolic rate was plus 47 and mounted again in one week to plus 66.

Continued bed rest and Lugol's solution was then carried out until on March 16, 1934 with a basal metabolic rate of plus 33, and a pulse rate between 88 and 115, partial thyroidectomy was performed, the right lobe of the thyroid being removed. The patient made an uneventful recovery and was discharged 10 days later with a basal rate of plus 42 and with orders to return after one month of rest.

She returned in one month and her basal metabolic rate was plus 60. She was operated on April 27, 1934 and the left lobe was removed with a small remnant of the isthmus. The convalescence was uneventful and at the time of discharge ten days later the basal metabolic rate was plus 14. A month later the patient reported that she felt perfectly well and for the first time in eight years she felt calm and had no palpitation.

This case illustrates the more severe form of thyroid intoxication which requires expert treatment. The added factor of thyroid toxemia superimposed upon a pre-eclamptic toxemia makes the case just that more difficult.

For purposes of this discussion the factor of pregnancy toxemia will be omitted. Had the case been <sup>seen</sup> earlier in the course of pregnancy the treatment would no doubt have been different. To begin with the thyroid toxicity was severe enough without the added load of pregnancy to warrant operation with no apparent relief. Second, the progress of such a severe syndrome would lead to a disastrous result if the average case had been handled as outlined above. Had this patient gone into a thyroid crisis the outcome would have been different. Third, surgical treatment was made very difficult since there had been previous radiation therapy which, according to Fleisher (18) is distinctly not indicated and since Lugol's solution had been administered with no regard to the immediate or remote effect. A toxicity of 8 years duration will certainly have some residual effect upon this woman. She has evidences now of a thyrotoxic heart. In such a case where the intoxication is so marked, thyroidectomy as her local surgeon advised 6 years ago, would have been the therapy of choice. Since this was refused the surgery should have been done soon after pregnancy was discovered in order that any added strain might have been prevented. However, to follow the advice of Mussey, Plummer and

Boothby (36) is very difficult since it cannot be determined just what effect pregnancy will have upon a toxic goiter.

### Treatment of Hyperthyroidism During Pregnancy

Of all the phases of thyroid disease in pregnancy, the two which have received the most consideration are the incidence and the treatment. Also, there are as many different ideas in regard to treatment as there are differences in the incidence throughout the world. A fact of interest is the evolution through which the ideas of treatment of this condition has passed. It was long ago observed that the ingestion of sea-weed in people with enlargements of the neck caused that enlargement to decrease in size. Out of this observation has come the use of iodine and later Lugol's solution as a method by which the size of the gland could be reduced but more important, a method by which the toxicity of the gland could be reduced even though it is only temporary.

Davidson (10) stresses the importance of preventive treatment before a woman reaches the child bearing period of life. It is well known what infection will do to a toxic goiter. Foci of infection should be removed and if necessary, radical treatment may be necessary. This is especially true in areas of endemic goiter.

The ideas of Gellhorn (22) have been mentioned above.

Of course his ideas are extremely radical and it is now known that the thyroid patient, though her chances for becoming pregnant have been reduced, has almost as good a chance for an entirely normal pregnancy and a normal baby as the woman without goiter. This has been brought about by an increase in the fundamental understanding of the pathological changes responsible for the condition and more thorough understanding of the treatment both surgical and medical. Also, the physician knows what he may expect in regard to the response the woman makes when she places an added load on an already toxic thyroid.

In reviewing the literature of the last few years, one is impressed immediately by the extreme differences which exist between the surgeon and internist as regards treatment. The argument seems to be as to whether a patient can be safely carried through pregnancy on medical management with or without Lugol's solution; whether it is fair to the patient to use Lugol's solution other than for the sole purpose of preparing her for thyroidectomy which may or may not be necessary later; and whether the use of Lugol's solution is contraindicated in the toxic adenoma. As will be pointed out later, the extremes may be quoted by authorities on these three questions.

There seems to be little difference in the general therapeutic measures employed either in a case of hyperthyroidism in pregnancy or in pregnancy incident to hyperthyroidism. Also the following general therapeutic measures are advocated by obstetrician, surgeon and internist.

To begin with the patient should be placed at complete bed rest if she is at all toxic. Her general condition should be watched with great care in order that all secondary infections might be prevented. If such infection should occur, strenuous treatment is required because the toxicity of the thyroid gland is more or less increased just as the diabetic responds to any infection. Her diet should be of an easily digestible type of high caloric value because the metabolic activities within the woman's body have been whipped up and more food is necessary since it is being used up more rapidly. The diet should be of low protein content, since protein has the highest specific dynamic action. Her fluid intake should be rather high since she perspires easily and has quite an excessive water loss in this manner. Another thing of importance is to divorce her from the strain of emotion if possible. These people have a distinct tendency toward emotional instability and anything which will pre-



precipitate any emotional attack should be avoided. Hospitalization in such cases is ideal. The patient's bowels must be kept in good condition but strenuous drugs should be avoided, substituting the gastrointestinal lubricants and low enemata.

An important part of the treatment consists of sedation. These women are extremely irritable and usually sleep poorly and should be helped along these lines. This is especially brought out by Fleischer (18) and Day (13) who advocate a warm glass of milk and a mild sedative such as bromide or phenobarbital at bedtime. This sedation should be continued during the day also so that the patients irritable nervous system is put more or less at rest.

Another general measure of importance which should be brought out is the fact that the second stage of labor should be reduced to the minimum with the use of forceps, and that abortion except in the judgment of Hinton (24) should never be done for two reasons. First it is not indicated with the newer methods of treatment, and second, it is dangerous in that thyroid crisis may be precipitated, as was pointed out by Lahey (27) in his

discussion on factors of mortality in thyroid disease which will be listed below. Xray and radium are not effective and should be avoided because it makes the operative procedure more difficult should it become necessary later. This is brought out by Lahey (27) and Davidson (10).

Should Lugol's solution be used? Bothe (5) of Chicago states that small doses of Lugol's solution are indicated if the patient is moderately toxic in order that this type of patient may be carried on through pregnancy. If this treatment is not effective plus the general medical management outlined above, the patient is placed into his surgical class and operated. His results have been excellent with the above routine. In the mild boarder line cases with very early symptoms, Bothe (5) feels should be operated early preceeded by iodine therapy to the point where the chances of a good result are maximum and thyroid crisis at a minimum. This he points out to be especially true in the toxic adenoma.

Mussey, Plummer and Boothby (36) point out in this connection the danger of giving iodine in appreciable amounts to patients who have adenomatous goiters of the

non toxic type or to patients more than 25 years of age who have diffuse colloid goiters because of the danger of initiating hyperthyroidism. It is quite probable that colloid goiters, at least the larger percent of them, contain non palpable adenomas. This advice is also given by Hinton (23) (24), Davis (11), (12) and Wallace (44) who add that iodine therapy used in adenomas for anything other than preparation for surgical treatment is wrong, since the toxicity of that adenoma may be made distinctly worse.

Yoakam (48) points out the importance of the use of iodine as a prenatal measure in regions of endemic goiter. He has made very scientific studies and shows the importance of monthly check ups on the thyroid gland which should be carried on through the post partum period. His studies included careful measurements of the isthmus of the thyroid glands of 937 patients but he concluded after this series that this method was not practical in following the progress of the patient and had no direct relationship to the toxicity of the gland in question. Another conclusion drawn from this work is the fact that iodine therapy did no good if given only in the last trimester of pregnancy.

The work of Plass and Yoakam (37) tends to show that the use of iodine given prophylactically during pregnancy is unable uniformly to prevent gestational hypertrophy of the normal thyroid gland but seems to be quite effective in preventing such a change in glands which are pathologically altered when pregnancy begins and may actually lead to a reduction in the size of certain of the colloid goiters.

Lahey (27) thinks that adenoma and exophthalmic goiter are a part of the same general pathologic process and this observation is borne out by Davis (12) who advises the use of iodine in toxic adenomatous goiter as well as the exophthalmic type and has seen no bad results in this connection. This observation is also made by Falls (17). All the writers (5), (8), (35), (12), (37), bring out the importance of the use of iodine in the treatment of hyperemesis gravidarum which may be in reality a manifestation of an early thyroid crisis. Bothe (5) treats all of his cases of persistent morning nausea and vomiting first by the use of Lugol's solution or thyroid extract. The use of thyroid extract in these cases seems to have originated in England and Germany and is not used so widely in the United States.

When should thyroidectomy be performed? This is probably one of the most difficult questions there is for the obstetrician to solve. His patient is at first placed in the hands of the internist who has a conservative regime in mind. The patient is put on a strict type of management with bed rest, sedation and Lugol's solution. If this type of therapy fails and the patient continues toward a more acute toxemia the surgeon is called in. The effects of Lugol's solution have been only slight and the surgeon is expected to operate and bring about a good result or else cure. These facts are brought out by Lahey (27) who lists seven factors in mortality in thyroid surgery. They are: (1) waiting, (2) age, (3) weight loss and lowered resistance, (4) infection with jump in toxic symptoms, (5) toxicity and not basal metabolic readings, (6) operative procedures other than thyroidectomy, (7) pregnancy when allowed to advance without operation, otherwise it is not a factor.

The above statements seem to indicate that radical treatment is the best. This conclusion is certainly not in accord with the observations of many observers on this question. Fleischer (18) considers thyroidectomy as indicated only if symptoms advance to an alarming degree.

He was compelled to do thyroidectomy only five times in 260 cases of Graves disease during pregnancy. In no case was he forced to interrupt pregnancy. This seems to be the general concensus of opinion as stated by Mussey and Plummer (35) who add that it is safer to remove a toxic adenoma rather than try to carry them through on iodine therapy and also that it is safer to do thyroidectomy before any symptoms referable to the heart have developed thus preventing any permanent damage to that organ. This conclusion is drawn by Day (13) and Wallace (44) who point out that the danger lies in the long continued thyrotoxicosis with a weakened heart. Wallace (44) cites the occasional case with onset during pregnancy which are rapid and fulminating in type and which require early operation. Day (13) stresses the importance of frequent post partum studies and the frequency of thyroid surgery necessary after delivery.

Gardiner-Hill (21) reports fatal termination in Graves disease during pregnancy as 50 percent and amelioration of symptoms which maintained after operation in 50 percent. This is certainly not in accord with the work of Mussey, Plummer and Boothby (36), Lahey (27),

Bothe (5) and Falls (17). Falls (17) has let some go with basal metabolic rates as high as plus 110 on medical management with good results. He points out that the surgeon is more or less in a bad position if the case should come to surgery later because of the inability of that patient to successfully respond to iodine therapy a second time. He also points out that there is a possibility even though it is remote, of producing hypothyroidism after operation before delivery when the extra load of pregnancy has been unloaded.

Fahrni (16) concludes that subtotal thyroidectomy should be performed if the patient is toxic and less than five months pregnant. After this time the patient should be carried through on medical management with the second stage of labor shortened and the thyroid surgery postponed till later. He advises against pregnancy for two years but does no abortions if pregnancy does occur. This is also the advice of Williamson (47). Hinton (23) (24) advises therapeutic abortion in cases of hyperthyroidism with myocardial involvement due to thyroid toxemia and in the fulminating type of thyroid dangerous to life. Frazier and Ulrich (20) and Polowe (38) point out the importance of removal of the adenomas because of pressure

on the recurrent laryngeal nerve and the trachea. They also advise the use of Lugol's solution after operation in an attempt to prevent return.

Much more has been written in the past three or four years concerning the etiology and prevention of thyroid disorders in the newborn than was written before this time. Not only should the woman involved be considered very carefully, but also her offspring. Davis (12) shows that iodine is present only in traces in infants thyroids unless the mother has been given iodine when it is enormously increased. He points out the importance of iodine therapy in preventing congenital goiter and cites a case in which the woman gave birth to a child with a congenital goiter after a gestation in which iodine was not a part of the prenatal care. The subsequent pregnancy with iodine as a prophylactic measure resulted in a normal baby. Yoakam (48) shows that 60 percent of infants born of mothers who had no iodine had enlarged thyroids and that there was no deviation from normal in the remaining 40 percent. After iodine therapy the incidence was reduced to 20 percent. After the introduction of iodized salt, the incidence in Detroit fell to 4 percent according to Yoakam (48). Clute and Daniels (8) report no



congenital goiters in infants born of thyrotoxic mothers. Plass and Yoakam (37) stress the importance of starting iodine therapy early in an attempt to prevent congenital goiter since no result can be obtained if the therapy is resorted to in the last trimester only. Hinton (23) (24) advises the use of iodine in colloid goiter in an effort to prevent fetal adenomata.

The subject matter in this disucssion has been most interesting. One is impressed by the wide differences of opinion which exist in the field and by the differences which one sees between foreign and American observers. Probably there is only one other complication of pregnancy about which there is more difference of opinion and that is the toxemias of pregnancy. When one observes the miserable state these people are in, a stimulation of the interest is immediate. Also the change one observes after radical treatment is startling, and even though these differences of opinion exist, the treatment is completely satisfactory.

### Conclusions

1. Thyroid hypertrophy during pregnancy is common.
2. Hyperthyroidism during pregnancy is rare because increased thyroid secretion causes a decreased activity of the ovary.
3. Pregnancy may improve an already toxic thyroid gland, there may be no change, or the thyrotoxicosis may be made distinctly worse.
4. Exophthalmic goiter occurs more frequently than toxic adenoma during pregnancy only because adenoma occurs at a later time in life when the child bearing period is, to a large extent, over.
5. The complications of thyroid toxemia require very careful consideration and vigorous treatment.
6. Colloid goiter presents no problem in treatment other than the administration of iodine or thyroid substance in order to prevent congenital goiter in the newborn.
7. In mild cases no treatment is required.

8. The dangers in adenoma seem to be not so much of those due to the toxemia itself, but more from the strain that pregnancy, labor, and delivery impose upon organs already damaged by a long continued toxemia.
9. In dealing with both toxic and non toxic adenoma during pregnancy, iodine or thyroid extract should never be used at any time or in any dose except as a preparation preoperative measure because of the danger of increasing a thyrotoxicosis already present or creating one in a dormant gland.
10. There is a distinct difference of opinion as to the best therapy in toxic cases between surgeon and internist.
11. The presence of pregnancy in thyrotoxicosis does not increase the operative risk of thyroidectomy.
12. Thyroidectomy in the first five months of pregnancy seems the treatment of choice. After this time, the patient should be carried through on medical management unless the toxicity of the gland should suddenly be increased when radical treatment should be instituted.
13. Hyperemesis gravidarum may be a manifestation of thyroid crisis and this type responds well to Lugol's

solution.

14. Abortion is practically never indicated as far as the thyrotoxic condition is concerned. Acute cardiac decompensation as a result of prolonged thyroid toxemia is certainly an indication.

15. The second stage of labor should be terminated as quickly as possible by the use of low forceps.

16. The best therapy is to foresee what is going to happen in a given case and direct treatment along those lines. If thyroidectomy seems inevitable, it should be done early.

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