PREGNANCY AND THE THYROID GLAND*

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The relation of thyroid activity to sex and its functions has long been recognized, but the particulars of this relationship have been subjects of endless speculation and conflicting hypotheses. Before presenting the few additional facts we have to offer, it may be well to review the facts already available and current opinions on the subject. Women are undoubtedly more susceptible than are men to all recognized functional disturbances of the thyroid gland, especially hyperactivity of the organ. The incidence of this latter condition appears to be greater during periods of changing sexual function—adolescence and the menopause. Concerning the effect of pregnancy there is some difference of opinion. It is generally agreed that the thyroid gland undergoes hyperplasia during pregnancy, but there is no certainty that this hyperplasia is attended by hyperfunction. The basal metabolism rises in the latter months of pregnancy,[8, 10, 19, 21] but the rate of oxidation is not controlled by the thyroid gland alone. The rise of basal metabolism in pregnancy is not accompanied by other recognized manifestations of hyperthyroidism. Indeed, serum cholesterol is said to increase, a phenomenon that is regularly observed in hypothyroidism.[1, 4, 6] The hypermetabolism of pregnancy is not regularly accompanied by the circulatory or nervous manifestations that characterize hyperthyroidism.

Clinical hyperthyroidism may begin during pregnancy, but this does not seem to be a frequent occurrence.[10] Clinical hyperthyroidism does not appear to influence the normal course of pregnancy nor to prevent conception. Thyroidectomized female animals are unable to conceive. Complete absence of the gland produces sterility in both sexes. This has given rise to the impression that infertility in women with normal menses may be due to some lesser degree of thyroid deficiency. Convincing evidence for such a concept has been hard to find, chiefly be-

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cause it is impossible, as Means[16] has pointed out, to diagnose with certainty minor or intermediate degrees of thyroid deficiency. It has been claimed by Litzenberg[12] among others that hypometabolism is found with unusual frequency in women who can not conceive and that administration of thyroid to such women may enable them to become pregnant. Hypometabolism, as he defines it, basal metabolism −10 or lower, is not acceptable evidence of hypothyroidism. Javert[10] has suggested that if hypothyroidism were a cause of infertility, hyperthyroidism might be expected to promote fertility. Actually, published reports indicate a low incidence of pregnancy among hyperthyroid subjects. He rightly points out that contraceptive practices may contribute to this rate.

Although total removal of the thyroid of the non-pregnant animal produces sterility; once pregnancy has been established, thyroidectomy does not interrupt it.[5, 7, 14, 15] Nevertheless, miscarriages, and especially the tendency to habitual abortion, have been attributed to hypothyroidism, and thyroid products have been given to prevent abortions.[11] Bodansky and Duff[2] claim that pregnancy makes rats more resistant to the effect of thyroid. This may bespeak a greater need for thyroid hormone during pregnancy; it can not be interpreted as evidence of hypothyroidism. Euthyroid subjects can often tolerate larger doses of thyroid than can patients with myxedema. The latter respond to active thyroid substance quantitatively, while animals with thyroid glands appear to be able to inactivate large amounts of such substance.[17, 23]

Finally—and here the evidence becomes more and more tenuous—thyroid deficiency has been held responsible for toxemias and other disorders of pregnancy.

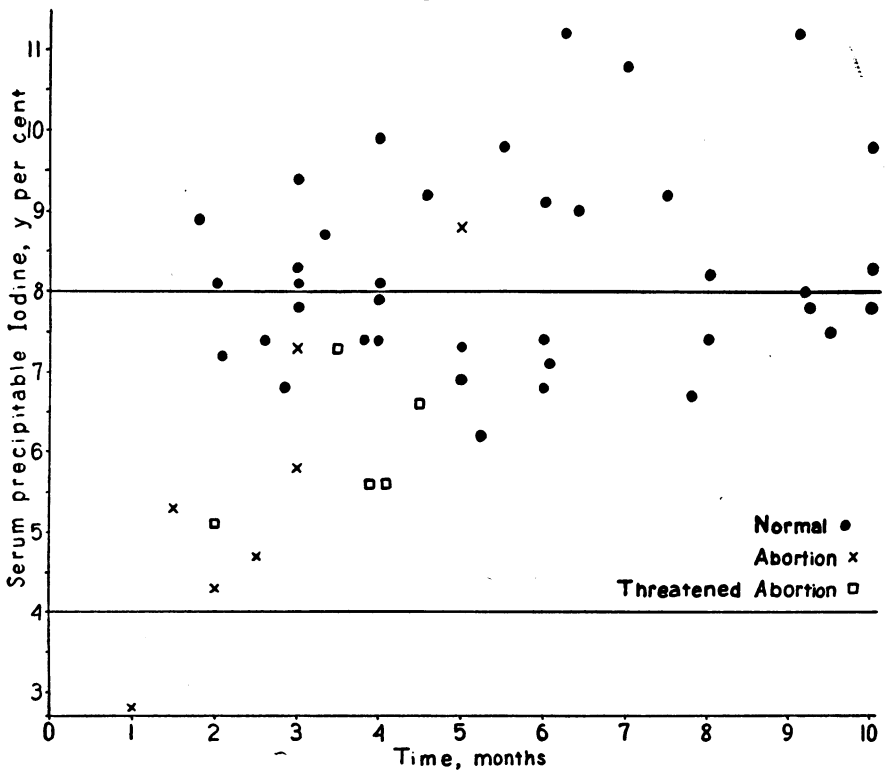
With accurate methods for the determination of serum iodine it seemed possible to resolve some of these uncertainties about the relation of thyroid activity to pregnancy and its complications. It has been demonstrated that in functional disorders of the thyroid gland the fraction of iodine which is firmly bound to the proteins of the serum, the precipitable iodine of the serum, reflects with great accuracy the activity of the gland. It appears to be uninfluenced by extraneous factors that affect the basal metabolism, serum cholesterol, and other functions that have been generally used as criteria of thyroid activity.[17, 18, 23, 24, 25] There is good reason to believe that most or all of the precipitable iodine of serum actually consists of thyroxine or active thyroid hormone. Thyroxine, when added to serum in vitro, attaches itself firmly to the proteins, behaving like the inherent precipitable iodine.[13] Recently Taurog and Chaikoff,[22] by the technique of isotope dilution, using

thyroxine labelled with radioactive iodine, have more directly identified the precipitable iodine of normal serum with thyroxine. The present report deals chiefly with the concentrations of precipitable iodine in the sera of pregnant women, measured by the method of Man, Smirnow, Gildea, and Peters.[13]

Results

In Figure 1 the circles indicate the concentrations of precipitable iodine in the sera of women with normal pregnancies that went to term. There are altogether 38 observations on 22 women from the second month to the day of delivery. The horizontal lines represent the limits of variation of precipitable iodine in normal, non-pregnant women, 4 to 8 γ per cent. The precipitable iodine of the pregnant women is dis-

Fig. 1



tinctly higher, ranging from 6.2 to 11.2 γ per cent. In fact, the average value, 8.3 γ per cent, is just above the maximum non-pregnant value. Further figures confirming these have been obtained, but are not shown

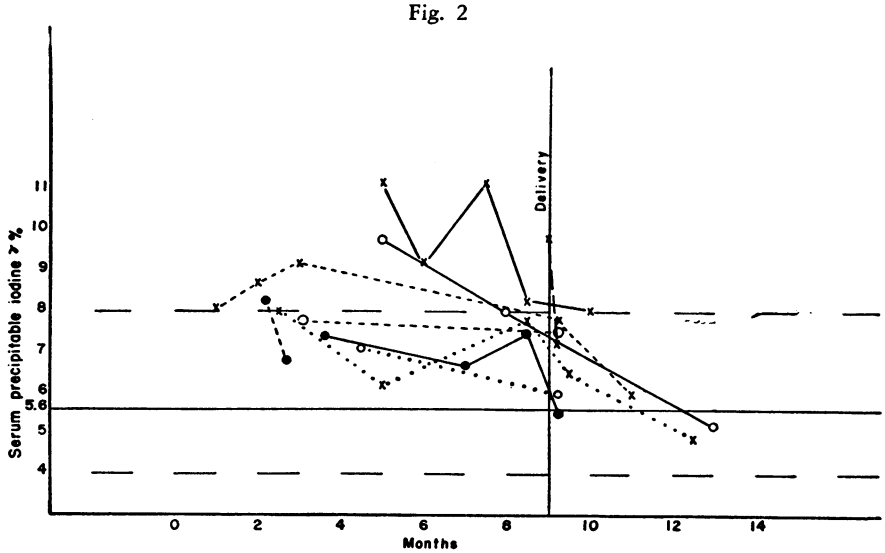
on the figure because the women from whom the sera were obtained have not yet come to term. None of these women presented symptoms or signs of hyperthyroidism. The elevation of iodine does not follow the course of the basal metabolism. The latter rises gradually after about the fourth month of pregnancy,[10, 19] whereas the precipitable iodine is already high as early as it is possible to make a diagnosis of pregnancy, as soon as the Ascheim-Zondek test is positive. Furthermore, although it may fluctuate somewhat in the course of pregnancy, it has, as far as can be determined from the data thus far collected, no tendency to deviate in one direction or the other as pregnancy progresses. This is another link in the chain of evidence that the rise of metabolism in the latter part of pregnancy can not be attributed to increased thyroid activity. Bokelman and Scheringer[3] in 1930 reported that the iodine of blood rises early in pregnancy. It is, of course, anomalous that a high concentration of thyroxine in the serum should not be accompanied by hypermetabolism. The question may even be raised whether this precipitable iodine is thyroxine or whether in pregnancy some other iodine compound without calorigenic influence may find its way into the serum. Whether or not this increment of iodine in pregnancy is thyroxine, the precipitable iodine does not rise further in the latter part of pregnancy, as might be expected if the increase of metabolism that characterizes that stage were induced by the thyroid.

Figure 2 shows the course of the serum iodine after pregnancy in a few cases. There is no evidence that the iodine falls before delivery, although the number of observations is too small as yet to warrant certainty on this point. Shortly after delivery it drops to the normal range. How soon this fall occurs is another question that requires further inquiry. From one or two of the observations in the series it would seem to be quite early and quite precipitate.

The crosses on Figure 1 represent patients who had miscarriages; the squares, patients who had bleeding of sufficient severity to warrant a diagnosis of threatened abortion. Eight of the twelve points lie below the concentration of 6.2 γ per cent, the lowest value found among the women with normal pregnancies that went to term. This is not a large number, but the arrangement of points on the figure could hardly be accidental. The reason the number is not larger is an illustration of the human factors with which clinical research has to contend. As soon as it seemed even possible that a low serum iodine might portend miscarriage, those responsible for the medical care of these women could not refrain from administering thyroid. The direct line of investigation

can, therefore, progress only as material is accidentally obtained. The data on this figure alone suggest that if the precipitable iodine of the serum is low early in pregnancy a miscarriage will probably occur. This impression is supported by the absence of low points after the fourth month. On the other hand, the presence of crosses and squares at iodine concentrations greater than 6 γ per cent means that low serum iodine is

Fig. 2

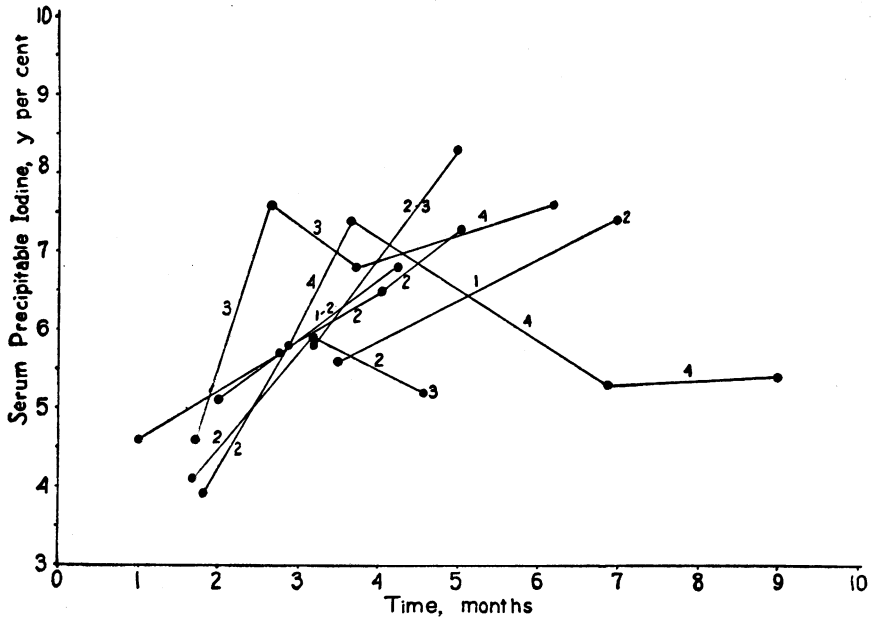


not the only cause of miscarriage. It remains to add that, just as the high iodines of normal pregnancy are not accompanied by symptoms or signs of hyperthyroidism, so the women with low iodines who aborted had no stigmata of hypothyroidism.

Certain inferential evidence has been gained in other ways. In Figure 3 is shown the course of the precipitable iodine of 7 patients who, having been discovered to have serum iodines below 6 γ per cent, were given various quantities of thyroid. In contrast to the patients in the first figure, the pregnancies of the women in this series proceeded without interruption, most of them to delivery (the remainder have not yet reached term). That such success can not be predicted consistently will be pointed out later in the discussion of one or two exceptional cases. It will be noted that in 4 instances the precipitable iodine did not rise above 6 γ per cent within the first 4 months of pregnancy. In every case, however, it did rise under the influence of thyroid therapy, approaching 6 γ per cent. The intervals between points are so long that the lines connecting them do not represent the course of the iodine, but only serve to

identify the values with the individual patients. Presumably the iodine in every case rose more rapidly. In only one woman did it rise above 8 γ per cent, although 2 received as much as 4 grains a day for considerable periods. This does not signify that these pregnant women had an exceptional tolerance to thyroid.

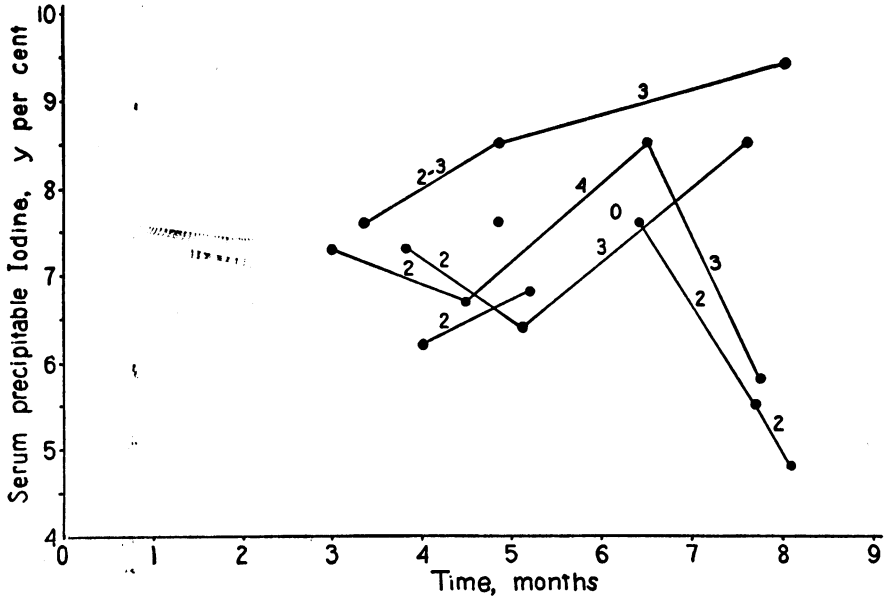
Fig. 3



In Figure 4 are shown a group of patients with serum iodines initially above 6 γ per cent who were, nevertheless, for various rather dubious reasons, given from 2 to 4 grains of thyroid daily. All were free from stigmata of thyroid dysfunction. The responses do not differ essentially from those elicited in patients with low initial serum iodine. In the second group, since iodine was higher in the beginning, it rose above 8 γ per cent more frequently. In both series, after prolonged administration of thyroid, precipitable iodine sometimes fell while medication continued. This again must not be interpreted as unusually high tolerance to thyroid because many apparently normal persons respond in the same manner. It may be noteworthy that when the iodine fell below 6 γ per cent in late pregnancy, the pregnancy was not interrupted. This suggests that in the more advanced stages low serum iodine is no obstacle to pregnancy. This should follow from the fact that in animals after pregnancy is well established thyroidectomy does not interfere with its progress. Chu[5] found that thyroidectomy in the

rabbit at an early stage of pregnancy caused resorption and abortion of the embryos, while at a later stage of pregnancy it resulted in the delivery of stillborn young. Apparently the latter is not true in other species. Chu's experiments do, however, indicate that the reaction to absence of thyroid differs as pregnancy progresses. The reaction in the early stages of pregnancy is like that which Chu noted when he succeeded in impregnating thyroidectomized rabbits.

Fig. 4



In Table 1 are shown the concentrations of iodine in the sera of patients who have had miscarriages, taken in the intervals between pregnancies and, in some cases, during pregnancies. In 10 cases the values during pregnancy were less than 6 γ per cent. On the other hand, only 2 out of 14, when not pregnant, had values lower than 4 γ per cent. In Table 2 are shown in the same manner the concentrations of iodine in the sera of patients who have had pregnancies without miscarriages. A few figures are higher than those from the group that had miscarriages, but the averages in the two tables differ by only 0.7 γ per cent. In one instance in the series without miscarriages the serum iodine was only 3.9 γ per cent. It is impossible from the concentration of iodine in the serum of a non-pregnant woman to predict with any certainty her reaction during pregnancy. From the first 3 cases for which

TABLE 1

PATIENTS WITH HISTORIES OF MISCARRIAGES

Name	*Serum precipitable I*		*Month*	*Remarks*
	Not pregnant	*Pregnant*		
	γ per cent	*γ per cent*		
Po	4.1	2.8	0.75	2 miscarriages
Sp	5.0	3.9	2.	2 miscarriages, 2 children
Mi		4.1	1.5	2 miscarriages, 2 children
Hor	5.6	4.6	1.5	2 miscarriages
Gi	5.5	4.8	1.5	On 1 gr. thyroid
Hi	3.8	5.1	1.5	2 previous miscarriages
Le	4.5	5.3	1.5	1 miscarriage
Is		5.4		1 miscarriage
Be	3.5	5.8	3.	1 miscarriage
Parm		5.8	3.	2 premature deliveries
Pars	5.1	6.3	2.	2 miscarriages
Bu		7.2	2.5	4 miscarriages
Zu		9.4	4.5	2 miscarriages, at 6 and 3.5 mos. This pregnancy has proceeded 9 mos.
Hol	5.5			2 miscarriages, 2 children
Jo	4.7			1 premature delivery at 6 mos.
Lyn	6.1			2 miscarriages
Lyo	5.5			2 miscarriages, 1 child
Na	5.8			2 miscarriages
Sh	5.1			Several miscarriages

both pregnancy and interpregnancy figures are given it may be seen that patients with relatively low iodine values in the interpregnant state have higher than normal values during pregnancy. In the group that had miscarriages the iodines rose but little during pregnancy when they did rise, and in some cases fell. This brings out the fact that failure of the iodine to rise in the normal manner during pregnancy does not bespeak an antecedent thyroid deficiency so far as this can be judged from serum iodine, but rather an improper reaction to the state of pregnancy. It is, of course, possible, indeed probable, that patients with deficient thyroid activity would have low serum iodine during pregnancy and a tendency to miscarriage.

In Table 3 are the serum iodines of women who sought advice because they were unable to become pregnant. Serum iodine was within normal limits in all. A surprisingly high normal value was found in one who had not menstruated for 8 years, while one of the lowest values

came from one whose fertility had been proved, although she had not been successful in expanding her family to the desired extent. This lends little support to the opinion that thyroid deficiency is a frequent cause of infertility, despite the fact that myxedema causes sterility.

TABLE 2

PATIENTS WITHOUT HISTORIES OF MISCARRIAGES

	Serum precipitable I		
Name	*Not pregnant*	*Pregnant*	*Month*
	γ per cent	*γ per cent*	
Mc	6.0	8.1	1.5
Eu	5.2	9.8	5.5
Sh	4.9	8.1	3.0

Not pregnant

Name	*γ per cent*	*Name*	*γ per cent*
Dl	6.2	Le	6.3
Fi	6.1	Ma	5.6
Bu	4.3	Ne	4.7
Ga	5.1	Qu	5.8
Hel	6.9	Re	3.9
Hu	4.3	Sm	5.7
Hes	5.2	Te	5.0
Joh	7.8	Th	6.8
Jos	7.5	Val	6.4
Pu	5.7	Van	5.7
Kr	5.0	Pr	4.1

TABLE 3

INFERTILITY

Serum precipitable I		*Remarks*
γ per cent	*γ per cent*	
5.7	5.7	
5.9	6.8	
5.5	5.4	
5.1	7.2	
4.6	4.8	
5.0	6.0	
5.3	6.4	
1.5	6.2	
4.2	7.9	Amenorrhea 8 yrs.
6.1	4.2	On thyroid gr. 1
		2 previous children

In Table 4 are 4 cases of toxemia serious enough to require termination of pregnancy, together with 2 cases of pyelitis in pregnancy. All had the higher serum iodines characteristic of normal pregnancy. The number of cases is too small to warrant any conclusions. It is, however, hard to conceive that toxemias, which are a manifestation of late pregnancy, could with any frequency be accompanied by low serum iodine if the latter leads to miscarriage in early pregnancy. If such a combination did occur, the natural inference would have to be, not that hypothyroidism provoked toxemia, but that toxemia caused serum iodine to fall.

TABLE 4

TOXEMIAS OF PREGNANCY

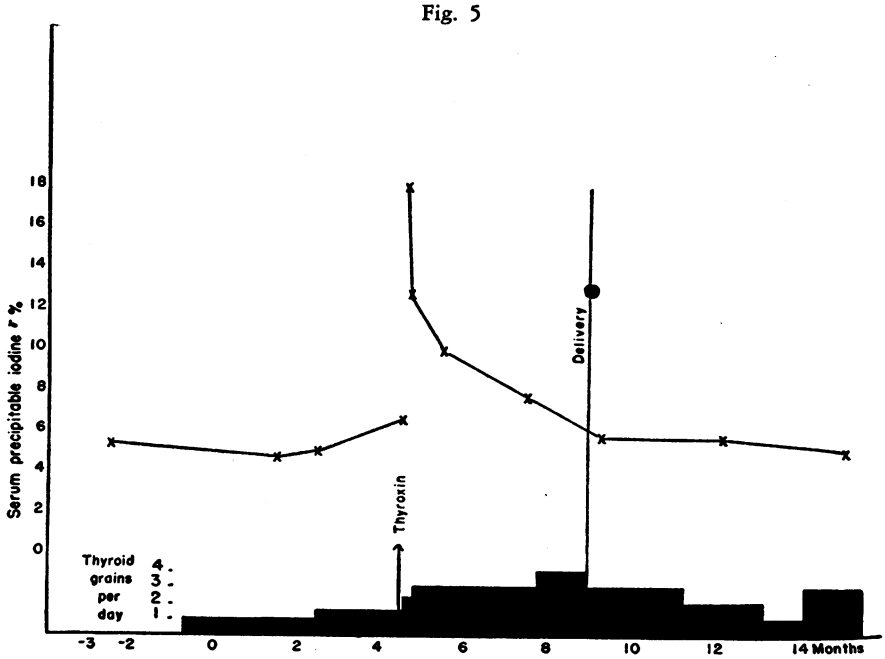
Name	*Month*	*Serum I*	*Remarks*
		γ per cent	
No	7.	8.4	Terminated 2 days later
Fo	2.5	8.3	Terminated 6 weeks later
He	2.	6.9	Previous toxemia. Terminated
Ro	2.	7.0	Previous toxemia. Terminated
Jos	8.	7.8	Pyelitis. Went to term
Joh	6.	8.2	Pyelitis. Went to term

Discussion

This must be considered as only a preliminary report and most of the deductions must be regarded as tentative hypotheses. The data are too incomplete to warrant definite conclusions. It does seem clear that for some reason the precipitable iodine of the serum rises during normal pregnancy. The evidence to date suggests also that if the serum iodine does not rise abortion is likely to occur in the early months of pregnancy. What relation the high serum iodine may have to activity of the thyroid gland is another question. It is possible that the increment in pregnancy is not, like the normal precipitable iodine, composed of thyroid hormone. Neither the patients with high nor those with low iodine have recognizable symptoms or signs of thyroid dysfunction. Serum lipids, which have been measured in a few cases, can not be correlated with iodine. This aspect of the subject is now under investigation. The best evidence that the precipitable iodine in pregnancy is thyroxine would be the demonstration that low serum iodine did interfere with the progress of pregnancy and that the administration of active thyroid substance both raised the serum iodine and prevented early abortion. Substantial, but not conclusive, evidence to this effect has been obtained. Three cases deserve especial description in this connection.

Gi (see Figure 5) had for some years, without good evidence of hypothyroidism, taken thyroid. During this period she had 2 normal pregnancies. After this she stopped taking thyroid. During this period she had three miscarriages. On June 29, 1945, while she was not pregnant and receiving no thyroid her serum precipitable iodine was 5.5 γ per cent, a normal figure. Her basal metabolism was −16 per

Fig. 5



cent, but she had no symptoms or signs of hypothyroidism, although she had not menstruated for a year. August 24 she was started on 1 grain of thyroid per day. September 15 she menstruated, but skipped her next period. November 1 the serum precipitable iodine was 4.8 and November 30 it was only 5.1 γ per cent. Pregnancy was suspected, but the Ascheim-Zondek test on December 11 was reported negative. The dose of thyroid was, nevertheless, increased to 1.5 grs. daily. February 3, 1946, when the serum iodine was 6.6 γ per cent, she began to have labor pains and bleeding. These stopped promptly after the intravenous administration of 2 mg. of thyroxine which was repeated on the following day. On February 6 the serum iodine was 18.8 γ per cent. She was given at this time 2 grs. of thyroid daily, which was increased to 3 and then to 4 grs. as the effect of the thyroxine wore off. She had a normal delivery on August 5.

Po did not menstruate until 15, and then for a time had scanty periods. For this reason, because she complained of lack of energy and because her basal metabolism was reported to be –44 per cent, she was given thyroid in gradually increasing doses up to 5 grs. daily, which she took until November 2, 1946. This had never caused symptoms of hyperthyroidism. At the time she stopped she was 3 months pregnant.

TABLE 5

Po, Born 1922. Married in 1945

1946

Nov. 2 — Stopped taking 5 grs. thyroid daily, 3 months pregnant.
Nov. 3 — Miscarriage.
Dec. 5 — Serum precipitable iodine 4.1 γ per cent.
Dec. 11 — Apparently normal menstrual period.
Dec. 30 — Serum precipitable iodine 2.8 γ per cent.

1947

Jan. 2 — Miscarriage.
Jan. 22 — Serum precipitable iodine 4.4 γ per cent.
Jan. 24 — 2 grs. thyroid daily.
March — Missed period.
Apr. 7 — 4 grs. thyroid daily.
Apr. 14 — 5 grs. thyroid daily.
Apr. 23 — Serum precipitable iodine 8.3 γ per cent.
June 3 — Serum precipitable iodine 10.0 γ per cent.
Sept. 15 — Serum precipitable iodine 8.6 γ per cent.
Nov. 15 — Spontaneous delivery.

The next day, November 3, she had a miscarriage. There is no intention of stressing this coincidence. On December 5, 5 weeks after discontinuing thyroid, the serum precipitable iodine was 4.1 γ per cent. On December 11 she had what appeared to be a normal menstrual period. On December 30 the serum iodine was only 2.8 γ per cent. January 2, 1947, she started to bleed and discharged material that proved histologically to be the product of another abortion. January 22 the serum iodine was 4.4 γ per cent. Two days later, on January 24, she was started on 2 grs. of thyroid daily. At this time she moved from New Haven to Cleveland. In March she missed a period. On April 7 her thyroid dose was raised to 4 grs. and on April 14 to 5 grs. daily. Subsequent serum iodines were: April 23, 8 γ per cent; June 3, 10 γ per cent; September 15, 8.6 γ per cent. November 15 she delivered spontaneously at term a normal girl.

Le had also taken thyroid for a time without definite evidences of hypothyroidism. Early in the summer of 1947 she had a miscarriage during her first pregnancy. October 20, while she was presumably not pregnant and was receiving no thyroid, her serum precipitable iodine was 4.5 γ per cent. November 24, after having skipped a period, she began to bleed. Her precipitable iodine at this time was 5.3 γ per cent. She was immediately started on 5 grs. of thyroid daily. The bleeding stopped. On December 29, in spite of this large dose, the iodine had

dropped to 4.8 γ per cent. The next day she delivered material that evidently indicated that the episode of November 24 had been not a threatened, but a missed abortion.

Granted that the increment of precipitable iodine in the serum during pregnancy is thyroid hormone, its significance is still enigmatical. What purpose does it serve? It apparently does not exert its usual action of accelerating metabolism. It does not rise progressively, as if it were utilized for the processes of new growth connected with pregnancy; but precipitately, as if it were concerned rather with the fundamental transformation that is pregnancy. That the pregnant woman is susceptible to the calorigenic effect of thyroid hormone is attested by the records of patients who have had spontaneous hyperthyroidism during pregnancy. It is worth remarking that subtotal thyroidectomy in this condition need not precipitate abortion. The present data indicate that the pregnant woman can tolerate considerable doses of thyroid without excessive rise of serum iodine or the appearance of toxic symptoms; but in this she does not differ demonstrably from a large proportion of her non-pregnant sisters. No one of the pregnant women in this series failed to react to doses of 2 to 4 grs. of thyroid; but Le took 5 grs. without any effect on her serum iodine after she had aborted. The pregnant woman resembles the non-pregnant in developing a tolerance for exogenous thyroid substance and a greater ability to dispose of it when it is given in large doses. This was pointed out in the discussion of the two instances in which serum iodine fell, after a preliminary rise, to low figures in two subjects who were taking, respectively, 3 and 4 grs. of dried thyroid daily.

It has been claimed that pregnant women require and excrete unusually large quantities of iodine.[20] Hertz and associates[9] have shown that the thyroid glands of pregnant rabbits take up radioactive iodine with unusual avidity. Both these observations indicate that the turnover of thyroid hormone is more rapid in pregnancy. If this were due merely to more rapid destruction or excretion of thyroxine, it should not manifest itself chiefly in increased serum iodine. Besides, the effects of thyroid administration do not indicate any increase in these processes alone. Nor do they reveal any striking difference in the reaction of the persons with high and with low iodines to exogenous thyroid. The latter do, however, appear to require greater amounts of iodine.

Conclusions

The precipitable iodine of the serum rises sharply at the onset of pregnancy from the normal concentration of 4 to 8 γ per cent to con-

centrations between 6 and 10 γ per cent, and remains at these levels until delivery, after which it rapidly returns to the normal range. This rise is not accompanied by other manifestations of increased activity of the thyroid gland. There is reason to identify the increment of iodine with the thyroid hormone.

There is evidence to suggest that failure of the precipitable iodine to rise at the onset of pregnancy leads to early miscarriage which may be prevented by the administration of active thyroid substance. Low precipitable iodine in these cases is not accompanied by other manifestations of thyroid deficiency.

The serum precipitable iodine in pregnancy does not appear to be consistently related to the concentration of iodine preceding pregnancy.

No evidence has been found in a limited number of observations that serum precipitable iodine is abnormal in women with infertility or suffering from toxemias of pregnancy.

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