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Research Article

THE PRECIPITABLE IODINE OF SERUM IN PREGNANCY COMPLICATED BY DISORDERS OF THE THYROID [1]

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In a series of papers (1–3) it has been shown that the precipitable iodine of the serum (SPI) rises in early pregnancy and remains elevated until delivery, thereafter returning to its usual concentration after a variable, but usually short, interval. Although SPI may rise to concentrations usually associated in nonpregnant women with hyperthyroidism, in pregnancy these rises are accompanied by no marks of excessive thyroid activity. In a large series of subjects without disorders of the thyroid, SPI was regularly below 7.8 γ per cent, in hyperthyroid subjects it was regularly above 7.2 γ per cent. Between these two points there was slight overlapping (4). In normal pregnancy, however, the majority of values lie above 7.2 γ per cent, with some as high as 10.0 γ per cent (3). The evidence indicates that failure of SPI to attain a concentration of about 6.0 γ per cent or higher within the first 16 weeks of pregnancy predisposes to miscarriage, and suggests that administration of active thyroid substances to women with low SPI early in pregnancy may avert miscarriage (3).

The significance of the elevated SPI is quite obscure. This increment is presumably composed of thyroid hormone. If it is hormone it still remains to discover whether the supply of hormone from the thyroid gland is increased, whether its utilization by the tissues is increased or diminished, or whether for some reason its combination with serum protein is unusually indissoluble. Other explanations of the phenomena can be conceived, but these serve to indicate the nature of the problem. Some indirect evidence may be secured by analysis of the behavior during pregnancy of patients with excessive or deficient thyroid activity. The present paper, therefore, deals with the course of SPI in pregnancy of 16 patients with disorders of function of the thyroid gland.

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MATERIAL AND METHODS

The 16 patients were all under the care of the Metabolism Clinic and staff. The majority were delivered on the Obstetrical Service of Yale University School of Medicine in the New Haven Hospital. A small number were delivered elsewhere. The procedures and methods have been already described (3).

Of the 16 patients nine were definitely hyperthyroid. Of these, one had two, and two had three pregnancies. One patient was definitely, a second probably, and three others questionably, hypothyroid. One patient when first seen in pregnancy had indubitable hyperthyroidism, but after three pregnancies became hypothyroid. The last of the 16 had questionable hyperthyroidism. In all cases the treatment was altogether medical, consisting of the administration of dried thyroid, Lugol's solution, and either thiourea or propylthiouracil. With few exceptions, which are noted in the protocols, patients received 14 or 15 drops of Lugol's solution daily while they were taking thio drugs.

PROTOCOLS OF CASES

Only features relevant to the subject of this paper are included in the following protocols.

B82863, born in 1917, had had a thyroidectomy for toxic goiter in 1939 and two operations for recurrences in 1946; one uncomplicated pregnancy in 1943, miscarriages in 1944 and 1946. When first seen, June 26, 1946, she had frank signs of hyperthyroidism with a diffuse goiter, slight exophthalmos, blood pressure 160/90, basal metabolism +26 per cent, and SPI 12.5 γ per cent. The record of SPI and antithyroid medication, beginning at this point, is illustrated in Figure 1. The course for 66 weeks preceding pregnancy is represented in broken lines to show the fluctuant character of the disease and SPI. During this period she was treated intermittently with Lugol's solution alone. When SPI was below 8.0 γ per cent she was free from signs and symptoms; when it rose above 8.0 γ per cent, hyperthyroidism manifested itself. The SPI of 8.8 γ per cent just before preg-

nancy 4 was accompanied by symptoms and apparently marked an exacerbation of her disease, since thio drugs were required thereafter. Throughout the pregnancy and the early postpartum period she seemed to be in a euthyroid state; but 16 weeks after delivery, with SPI 10.3 γ per cent, there were signs of overactivity of the thyroid. Nevertheless, medication was stopped. She was evidently in a relapse 11 weeks before pregnancy 5 with SPI 18.4 γ per cent. This responded rapidly to propylthiouracil, the dose of which had to be reduced in the course of the pregnancy. Symptoms of hyperthyroidism did not recur until after 26 weeks and following interruption of the drug for two weeks SPI reached 13.2 γ per cent. Symptoms ceased again shortly after the SPI of 10.3 γ per cent at the end of 31 weeks.

The hyperthyroidism in this case evidently progressed in severity during the period before pregnancy 4. The outburst of hyperthyroidism before pregnancy 5 can be attributed to inadvised discontinuation of therapy. The doses of thio drugs used in the two pregnancies are not so different as the figures would indicate because of the greater effectiveness of a given weight of thiourea. The initial dose was probably greater in pregnancy 5 while the later dose was greater in pregnancy 4 until the last period of 5 when the dose of propylthiouracil was increased to 100 mg. This may account for the differences in the two pregnancies. On the whole, however, the general similarity of the course of SPI is more striking. It fell rapidly in the early part of both pregnancies, despite diminishing doses of thio drugs, until it reached values lower than those usually encountered in pregnancy, rising again in the latter half of pregnancy. The sequences are complicated by the fact that the patient was in a hyperthyroid state just before both pregnancies. Initial treatment was obviously overvigorous at first and, in pregnancy 5, too light later. The complete withdrawal of propylthiouracil in this pregnancy was an error of clinical judgment. The rises of SPI as pregnancy advanced may have been due in part to the influence of pregnancy itself. In both pregnancies the patient remained free from symptoms when SPI lay between 8 and 10 γ per cent, the range for normal pregnancy, although symptoms of hyperthyroidism had appeared with SPI in the region of 8 γ per cent when she was not pregnant. This tolerance persisted for an interval after delivery in both instances, while SPI remained elevated. Subsequently, after pregnancy 4, hyperthyroidism appeared, with a further rise of SPI.

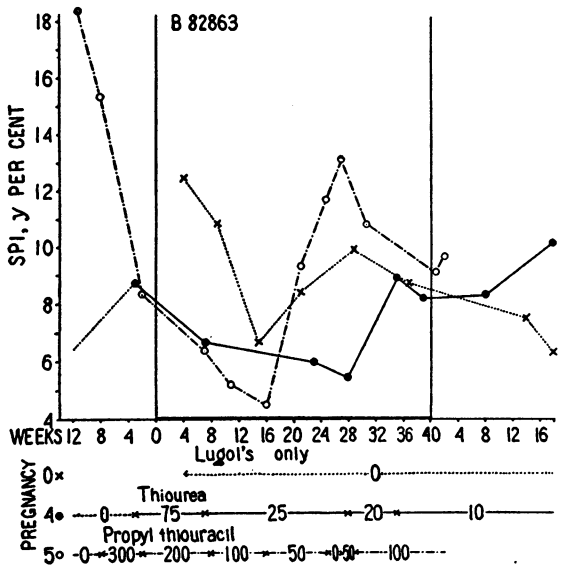

FIG. 1. THE COURSE OF SPI OF A HYPERTHYROID PATIENT BEFORE AND DURING TWO PREGNANCIES

The period of pregnancy is defined by the two vertical lines. It is arbitrarily set at 40 weeks after the last menstrual period, 0 weeks. Observations are also dated from this period. The interval between the last observation in pregnancy and delivery is not, therefore, precise, since delivery did not always occur after exactly 40 weeks. Periods before and after pregnancy are indicated to the left and right of the pregnant area, respectively. Therapy is indicated by the figures below the chart, the lines and arrowheads indicating the duration of each dose.

In this particular case the broken line with solid dots does not represent a pregnancy, but a continuous period of 72 weeks preceding her fourth pregnancy during which the patient received only Lugol's solution (see protocol).

B50050, born in 1922, had normal deliveries in 1941 and 1942, miscarriages in 1941, 1942 and about July of 1945. Symptoms of hyperthyroidism began early in 1945. When first seen in March, 1946, she had diffuse enlargement of the thyroid, slight exophthalmos, frank hyperthyroidism, basal metabolism +68 per cent and SPI 24.2 γ per cent. The course of SPI and therapy, beginning with this point, which just preceded pregnancy, is illustrated in Figure 2. After six weeks, with SPI down to 9.3 γ per cent, symptoms and signs of hyperthyroidism had subsided. In neither pregnancy did symptoms or signs recur until the sharp peaks of SPI at 10 and 11 weeks postpartum, respectively.

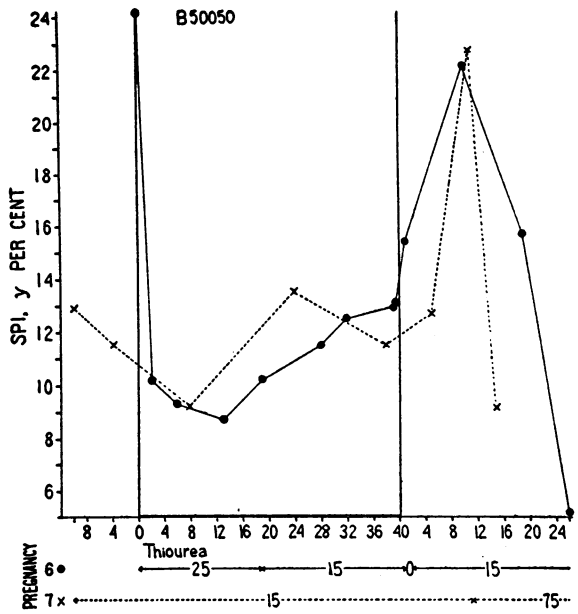

FIG. 2. THE COURSE OF SPI OF A HYPERTHYROID PATIENT IN TWO SUCCESSIVE PREGNANCIES

The general significance of the symbols is described in the legend to Figure 1. Only a part of the interval between pregnancies is illustrated.

The similarity of the course of SPI in these two pregnancies seems too close to be ascribed to coincidence. The slight early decline and the late rise resemble the reactions of the preceding case (B82863), but the picture is not distorted by changes of therapy or the severity of the thyroid disorder, which appears to have remained relatively stable. The impression is derived that in pregnancy hyperthyroidism can be more easily controlled. In this sense hyperthyroidism is not synonymous with SPI which appears to follow a course similar to that characteristic of pregnancy in euthyroid subjects, but perhaps at a higher level. The outbursts of hyperthyroidism after each delivery suggest a discharge of activity after the release of the inhibitory effect of pregnancy. The figures in the later part of pregnancy are so high as to indicate that this condition conferred a degree of tolerance for thyroid hormone (or SPI) greater than the similar tolerance of euthyroid pregnant subjects. In this case, however, this can not be definitely substantiated. Just before pregnancy 7, while the patient appeared to be in a euthyroid state, values of 12.9 and 11.5 γ per cent were observed.

B35786, born in 1922, had a normal pregnancy in 1943. In 1940 and in 1944 she was given small doses of thyroid because of increasing weight and lethargy. Symptoms of hyperthyroidism appeared early in February, 1946. She was seen March 7 of that year, four weeks pregnant, with moderate enlargement of the thyroid, typical manifestations of hyperthyroidism, basal metabolism, + 56 per cent and SPI 23.1 γ per cent. Her course, beginning with this point, is illustrated in Figure 3. There was a temporary sharp fall of SPI, but symptoms were not allayed and basal metabolism remained elevated until about the 24th week. She was again distinctly hyperthyroid 11 weeks after delivery when SPI had shot up to 23.8 γ per cent and continued to have symptoms, except during a short remission when SPI fell to 6.2, until pregnancy 3. In the first part of this pregnancy, which terminated in a spontaneous miscarriage after 23 weeks, hyperthyroidism was not allayed and SPI rose, probably because the patient was unable by reason of nausea to take her medication. Three days after the miscarriage (the interval in the figure is not real, but represents only transition from pregnancy to the postpartum state) basal metabolism was + 3 per cent and SPI had fallen to 11.1 γ per cent. Thirty-five weeks after the miscarriage she was again thyrotoxic and came into pregnancy 4 in this state. She became euthyroid, however, shortly after pregnancy began and remained in this state as long as she was followed.

In this case again, after the initial hyperthyroidism was controlled, SPI declined steadily in both pregnancy 2 and pregnancy 4, remaining, however, always above nonpregnant euthyroid con-

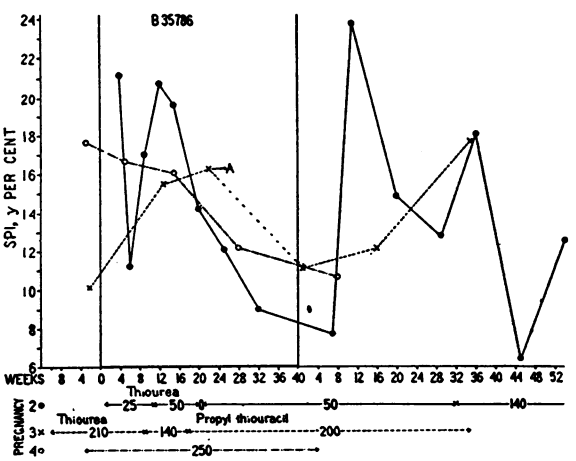

FIG. 3. THE COURSE OF SPI OF A HYPERTHYROID PATIENT IN THREE SUCCESSIVE PREGNANCIES

The general significance of the symbols is described in the legend to Figure 1. Pregnancy 3 ended in abortion at the point *A*. The interval between this and the vertical line marking the end of pregnancy does not indicate actual elapsed time. The next observation was made one week after the abortion.

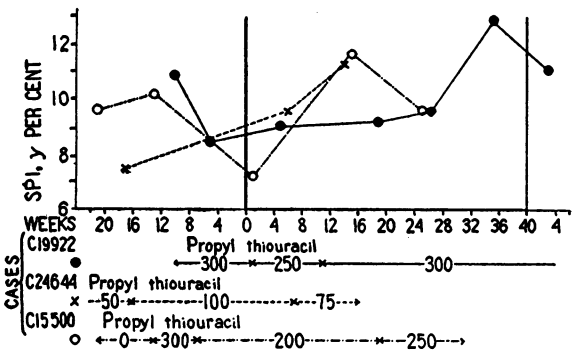

FIG. 4. THE COURSE OF SPI OF THREE HYPERTHYROID PATIENTS DURING PREGNANCY

The general significance of the symbols is described in the legend to Figure 1.

centrations, suggesting that the requirement for thio drug diminished. Pregnancy 3 can not be evaluated. The course of SPI might suggest that the hyperthyroidism was exacerbated, the rise of SPI can probably be attributed to her failure to take her medication. After pregnancy 2 she had an outburst of hyperthyroidism associated with a sharp rise of SPI quite similar in degree and time to those of the preceding case. This only partly subsided spontaneously. Although no sharp spike was noted after pregnancy 3, SPI rose after pregnancy. At 36 and 35 weeks, respectively, the values for SPI after pregnancies 2 and 3 were almost identical. The patient appeared to tolerate while pregnant values of SPI higher than those tolerated even during pregnancy by normal persons.

C19922, born in 1913, when first seen on January 4, 1949, had four children, the oldest 11. Symptoms of hyperthyroidism, which began four months earlier, were characteristic, including a slight goiter and mild exophthalmos, basal metabolism +34 per cent and SPI 10.9 γ per cent. Her course beginning at this point is illustrated in Figure 4. Symptoms were rapidly allayed, but recurred when the dose of thiouracil was reduced during the early part of pregnancy.

C24644, born in 1914, developed symptoms of hyperthyroidism shortly after a normal delivery in 1946. When first seen, April 16, 1948, after she had taken 150 mg. of propylthiouracil daily for three weeks, she was still definitely hyperthyroid, with a diffusely enlarged thyroid and SPI 7.1 γ per cent. On Lugol's solution and 50 to 125 mg. of propylthiouracil daily, symptoms and signs were kept in abeyance and SPI within normal limits until the onset of her pregnancy, January 17, 1950. The record in Figure 4 begins 17 weeks before this. Although, after the onset of pregnancy, without change of medication, SPI rose, she remained euthyroid.

C15500, born in 1920, had a normal pregnancy in 1946. In 1942 she developed hyperthyroidism, which recurred after a thyroidectomy in 1944. When first seen, August 30, 1948, she had mild symptoms of hyperthyroidism and SPI 9.6 γ per cent. The course beginning with this point is illustrated in Figure 4. Symptoms subsided rapidly after propylthiouracil was begun. Thereafter, with the exception of a short interval at about 16 weeks when SPI was 11.7 γ per cent, she seemed euthyroid.

SPI in the three cases illustrated in Figure 4 remained at more moderate concentrations than it did in the three preceding cases. The observations were, however, limited. In all, insofar as they were studied, SPI tended to rise as pregnancy advanced. With these rises C19922 and C15500 developed or retained some symptoms and signs suggestive of continued overactivity of the thyroid. These are the only patients in the series who had such manifestations while SPI was below 10 γ per cent. In contrast, SPI of C24644 rose during pregnancy, without evidences of hyperthyroidism, to concentrations far above those that before pregnancy had been associated with symptoms.

C38870, born in 1919, had an uncomplicated pregnancy in 1942. At that time she was given 0.03 gm. of thyroid daily. In November, 1944, she developed symptoms of hyperthyroidism, accompanied by urticaria, angioneurotic edema and bronchial asthma. When seen in this condition September 9, 1945, her basal metabolism was +36 per cent, SPI 10.4 γ per cent. The record of her course in Figure 5 begins eight weeks before the onset of pregnancy, which began June 15, 1949. In spite of the steady rise of SPI during pregnancy, she had no evidences of hyperthyroidism until eight weeks after delivery when SPI was 16.1 γ per cent.

B87633, born in 1909, had normal pregnancies in 1940 and 1943. After a thyroidectomy in 1940, hyperthyroidism recurred in 1945. When first seen, May 29, 1946, 23 weeks after the beginning of pregnancy, she had a diffuse goiter, basal metabolism +24 per cent and SPI 13.3 γ per cent. Her course beginning with this point is illustrated in Figure 5. She had a remission of symptoms shortly after medication began and just after delivery, corresponding to the low SPI's, but had a slight recurrence of thyrotoxicosis just before delivery and a more obvious one eight weeks after delivery.

ST, born in 1918, developed hyperthyroidism in 1944. When first seen, May 8, 1947, taking probably 150 mg. of propylthiouracil and 15 drops of Lugol's solution daily, her thyroid was moderately enlarged, but she had no signs of hyperthyroidism. SPI proved to be 1.9 γ per cent. The course, beginning with this point, nine weeks before pregnancy, is illustrated in Figure 5.

With reduction of the dose of propylthiouracil SPI rose quite slowly at first, but between 11 and 16 weeks jumped from 4.9 to 9.2 γ per cent. Just before delivery, the dose of propylthiouracil was increased because of transitory equivocal symptoms of hyperthyroidism: palpitation and sweating, but no tachycardia, basal metabolism + 5 per cent and SPI 8.3 γ per cent. With the SPI 20.6 γ per cent 12 weeks after delivery she was frankly hyperthyroid with pulse rate 102 and basal metabolism + 55 per cent. The infant at birth had a large goiter. This will be discussed in another communication.

The three cases in Figure 5 suggest again that the requirement for thio drugs, estimated by clinical criteria, diminishes, although SPI may rise, as pregnancy advances. They also suggest that SPI may rise higher in pregnancy and for a short interval after pregnancy than in the nonpregnant state, without evidence of hyperthyroidism. They also suggest that the hyperthyroid patient can tolerate higher values than the euthyroid subject can during pregnancy. In case C38870 reduction of thiourea from 75 to 25 mg. may have been unwarranted. Nevertheless, it resulted in no precipitate rise of SPI, but a gradual, symptomless ascent from 8.4 to 12.1 γ per cent. Case B87633, on 15 mg. of thiourea daily, was not unquestionably euthyroid when SPI fluctuated between 13.3 and 10.2 γ per cent; but, after the first observation, signs of hyperactivity were minimal. After delivery all three patients developed hyperthyroidism, C38870 and B87633 without change of therapy, ST despite an increased dose of thiourea. In B87633 these symptoms were not associated with a greatly elevated SPI, but in the other two patients they were. ST exhibited a sharp peak similar to those observed in B50050 (Figure 2) and B35786 (Figure 3) at approximately the same interval after delivery. ST, when first seen, was evidently approaching myxedema. Reduction of the dose of propylthiouracil to 100 mg. raised SPI only to 4.9 γ per cent in 15 weeks. At the end of that time, however, it rose abruptly without change of therapy, behaving like that of a normal pregnant woman.

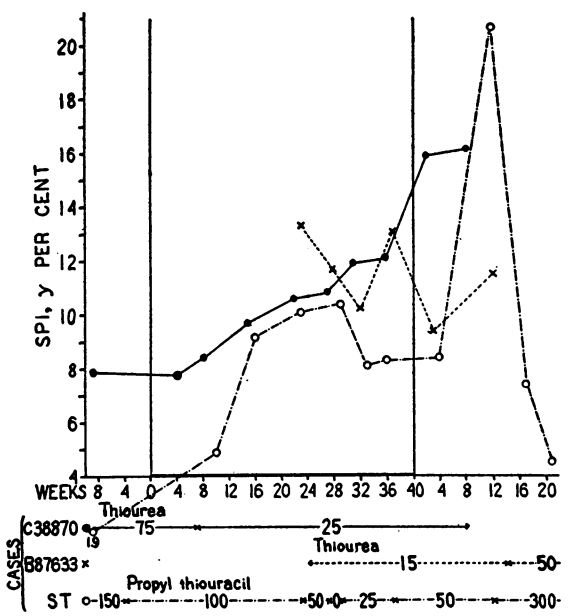

FIG. 5. THE COURSE OF SPI OF THREE HYPERTHYROID PATIENTS DURING PREGNANCY

The general significance of the symbols is described in the legend to Figure 1.

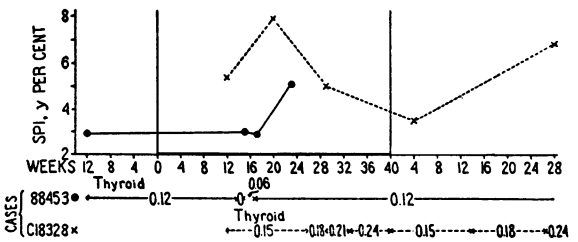

FIG. 6. THE COURSE OF SPI OF TWO HYPOTHYROID PATIENTS DURING PREGNANCY

The general significance of the symbols is described in the legend to Figure 1.

88453, born in 1919, had a pregnancy in 1938. In 1939 she noted increasing weight, puffiness of the eyelids and legs, and increasing fatigue. When first seen on September 16, 1942, she presented classical signs of myxedema. SPI was 0.4 γ per cent, basal metabolism − 33 per cent and serum cholesterol 249 mg. per cent. On 0.12 gm. of thyroid daily her condition improved rapidly, SPI varying from 3.0 to 5.4 γ per cent, basal metabolism from − 14 to + 7 per cent, in the next 15 months. She became pregnant January 1, 1944. SPI 11 weeks before this was 2.9 γ per cent. Her course, beginning with this point, is illustrated in Figure 6. Subsequent SPI's in 1949, while she was still taking 0.12 gm. of thyroid, were 3.0 and 3.4 γ per cent. Clinically she remained euthyroid throughout pregnancy on the same dose of thyroid that she took when not pregnant.

C18328, born in 1922, in 1944 noted increasing weight, somnolence, lassitude, dry nails and brittle hair. In 1945, 0.06 gm. of thyroid daily, given because her metabolism was − 26 per cent, restored her to a normal state. When she stopped the thyroid that summer symptoms recurred, basal metabolism falling to − 28 per cent. She was given 0.12 gm. of thyroid, which was increased

in March, 1946, to 0.15 gm. daily. When first seen on November 15, 1948, after the 12th week of pregnancy, she appeared normal in all respects, with SPI 5.4 γ per cent and basal metabolism − 11 per cent. The record in Figure 6 begins with this point.

Of the two cases illustrated in Figure 6, one, 88453, had frank myxedema; the second probably had hypothyroidism. Unfortunately, the observations on both, in and about pregnancy, are scanty. Case 88453 had extremely low SPI's at 15 and 17 weeks, 3.0 and 3.4 γ per cent, respectively. This would seem to indicate that such values are not incompatible with completion of a normal pregnancy. She had, however, omitted thyroid for nine days before the first of these and had taken an inadequate dose in the interval of three weeks before the second. The two low values may, therefore, represent a transitory drop. With resumption of a proper maintenance dose, SPI at the next observation was 5.1 γ per cent and may have risen farther as pregnancy advanced. Case C18328, when first seen in pregnancy, had an SPI of 5.4 γ per cent that rose, at the end of eight weeks, without change of therapy, to 7.9 γ per cent. In the later part of pregnancy it had fallen to 5.0 γ per cent, although the dose of thyroid had been increased. Unfortunately, no further observations were made until after delivery when, on the original dose of thyroid, SPI was 3.5 γ per cent. This patient was never seen when she was not taking thyroid. The story of her initial symptoms and her reactions to administration and withdrawal of thyroid seem characteristic of hypothyroidism. Nevertheless, SPI was never subnormal. Furthermore, it rose spontaneously under the stimulus of pregnancy, as it does in normal persons, without change of therapy, and fell after delivery. Finally, she was able after delivery to tolerate 0.24 gm. of thyroid without clinical evidence of hyperthyroidism, which is unusual for a hypothyroid subject. The effect of this dose on SPI was, unfortunately, not ascertained. Even 88453, with indubitable hypothyroidism, seemed to be able to raise SPI under the stimulus of pregnancy.

B90834, born in 1924, in 1940 was given up to 0.30 gm. of thyroid daily for obesity. This dose was later reduced to 0.12 gm., and in 1945 discontinued entirely for eight months, without noticeable effects. Thyroid was again resumed in a dose of 0.09 gm. because the basal metabolism was − 16 per cent, with the idea that

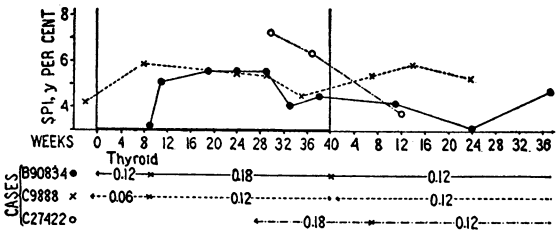

FIG. 7. THE COURSE OF SPI OF THREE QUESTIONABLY HYPOTHYROID PATIENTS DURING PREGNANCY

The general significance of the symbols is described in the legend to Figure 1.

it might promote conception. In 1947 she had a normal delivery after an uneventful pregnancy. November 3 of the same year her basal metabolism was − 17 per cent. December 23 thyroid was discontinued. January 13, 1948, she had a prolonged menstrual period at the normal interval. Because a spontaneous abortion was suspected, she was ordered to resume 0.12 gm. of thyroid daily, despite the absence of evidences of hypothyroidism. On several occasions after this, because of irregular bleeding, pregnancy was suspected, but the Ascheim-Zondek test remained consistently negative. March 3 the dose of thyroid was increased to 0.18 gm., but within a month was again reduced to 0.12 gm. and finally, on October 18, was stopped entirely. The interruption coincided with her last menstrual period. December 20, when the first SPI was 3.2 γ per cent, she had been pregnant for nine weeks and had been taking 0.12 gm. of thyroid for five weeks. The course, beginning with this point, is illustrated in Figure 7.

C9888 was born in 1927. In 1940, because she lacked vigor, was somewhat somnolent and had oily skin, a basal metabolism was taken and found to be low. In 1942 her condition appeared to improve when she took 0.06 gm. of thyroid daily. In January, 1947, just before marriage, she discontinued medication with no other effect than slight retardation. January 22, 1948, she became pregnant. Her SPI two weeks earlier was 4.2 γ per cent, basal metabolism − 16 per cent. Her course, beginning with this point, is illustrated in Figure 7.

C27422, born in 1920, in 1947, because of lassitude, infertility and a basal metabolism of − 23 per cent, was given 0.12 to 0.18 gm. of thyroid daily. She noticed little change in her symptoms, but her basal metabolism rose to − 5 per cent, to fall again to − 17 per cent when she discontinued medication. She, therefore, resumed thyroid, taking from 0.03 to 0.12 gm. daily.

She became pregnant February 26, 1949. May 31, since she had no signs of thyroid disorder, the thyroid was discontinued. June 27, because her basal metabolism was − 19 per cent, she was given 0.09 gm. of thyroid daily, which was progressively increased until on September 8 it was 0.18 gm. September 26, at the end of 30 weeks of pregnancy, SPI was 7.3 γ per cent, pulse rate 72. The course, beginning with this point, is illustrated in Figure 7.

The three patients in Figure 7 at one time or another received thyroid for presumptive hypothyroidism, although it is doubtful whether this diagnosis was justified. SPI of B90834 and C9888, on moderate doses of thyroid, rose in the early months of pregnancy to concentrations of 5.6 to 5.9 γ per cent, slightly lower than those usual in pregnancy, falling in the later part of pregnancy without change of therapy. The course of C27422 can not be distinguished in any respect from that of a normal pregnant woman. The trio emphasized what was brought out in an earlier paper (3), the ability of the pregnant woman to dispose of thyroid hormone.

A16616, born in 1907, on June 24, 1942, when she was six weeks pregnant, though free from symptoms, was found to have a palpable thyroid gland, slight exophthalmos, a pulse rate of 92, basal metabolism +35 per cent and SPI 11.2 γ per cent. Her course, beginning at this point, is illustrated in Figure 8. She was followed altogether through three pregnancies and the intervals between them, receiving variable, sometimes intermittent, doses of Lugol's solution. Her course throughout resembled that of a normal woman. There were never clinical manifestations of hyperthyroidism and the pulse rate did not exceed 80.

C15718, born in 1926, in 1945 noted enlargement of her thyroid gland. In 1946 she had a normal pregnancy. When seen September 2, 1948, she had a moderate, diffuse enlargement of the thyroid, rather dry hair, a pulse rate of 68, basal metabolism −22 per cent, SPI 3.8 γ per cent and serum cholesterol 197 mg. per cent. Her course, beginning with this point, is illustrated in Figure 8. There was nothing unusual about her course until 14 weeks after delivery when she was found to be gaining weight rather rapidly, her pulse rate was only 52 and she complained of pains in the upper part of her chest and feeling bloated after meals. One month later her weight had increased further, her skin had become dry and her face and hands seemed puffy. Serum cholesterol proved to be 358 mg. per cent (unfortunately the tube containing the specimen for determination of SPI was broken). She was given at once 0.12 gm. of thyroid, which was increased to 0.18 gm. daily four weeks later, because her symptoms had not been entirely allayed. April 10, 1950, two months after the thyroid was begun, SPI was 6.3 γ per cent, serum cholesterol 135 mg. per cent, pulse rate 70, weight normal, and she felt and appeared euthyroid.

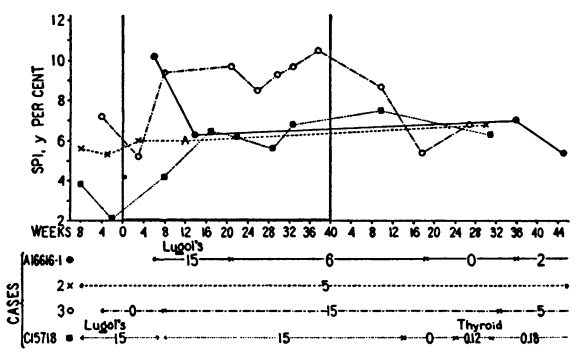

FIG. 8. THE COURSE OF SPI OF TWO QUESTIONABLY HYPERTHYROID PATIENTS DURING PREGNANCY

The general significance of the symbols is described in the legend to Figure 1. Case A16616 was followed through three pregnancies. The figures for therapy refer to drops of Lugol's solution except at the end of the course of Case C15718 when thyroid was substituted.

These two cases illustrated in Figure 8 are quite anomalous. There can be little doubt that A16616 had hyperthyroidism when she was first seen. Both SPI and evidences of hyperthyroidism subsided under the influence of Lugol's solution alone. Thereafter she ran a clinically almost euthyroid course in and out of pregnancy, with and without Lugol's solution in variable doses. On one occasion, after the third delivery, moderate signs of overactivity of the thyroid appeared with SPI 8.0 γ per cent, while she was receiving 5 drops of Lugol's solution daily. These subsided without change of therapy, SPI falling to 5.5 γ per cent, and subsequently to 3.4 γ per cent while she was taking no medication. The basal metabolism also was most capricious, usually above normal, with no apparent relation to SPI or clinical condition. This is a most abnormal pattern of behavior. Whether it indicated fluctuant thyroid activity it is impossible to say. Whatever its significance may have been, in pregnancy SPI followed the course expected in a euthyroid subject.

Case C15718 was given Lugol's solution in behalf of a goiter only. Shortly thereafter, just before pregnancy, SPI fell to 2.1 γ per cent, a concentration indicative of hypothyroidism. Nevertheless, it rose in pregnancy and remained elevated until 14 weeks after a normal delivery, when she suddenly developed hypothyroidism. It is possible that she was entering this state before pregnancy. In this case it must be inferred that the stimulus of pregnancy was able to elicit a response from the failing gland.

DISCUSSION

Certain difficulties present themselves in the analysis of these data. Hyperthyroidism is inherently a variable disease, marked by remissions

and exacerbations. In many instances there was no opportunity to observe the behavior of the patients for extended periods outside of pregnancy. Sometimes only fragments of the courses during pregnancy could be studied. Often it was not feasible to make observations at frequent or consistent intervals. The most desirable intervals for observations, indeed, were not known. It has been pointed out that SPI fluctuates greatly during normal pregnancy (3). It was impossible to follow any consistent course of therapy with justice to the patients; the treatment had to be regulated in accordance with the presumptive needs of each patient. In the earlier phases of the study the peculiar behavior of SPI during pregnancy was unknown. Attempts were, therefore, made to keep SPI within normal, nonpregnant limits. These were, however, somewhat tempered by fear for the consequence to the fetus should thyroid function be too much depressed. Efforts to strike a golden mean were not entirely successful. Recognition of the facts about SPI in pregnancy only complicated the problem. The last purely objective measure of thyroid activity was removed. Both basal metabolism and serum lipids are variously affected by pregnancy and are not, therefore, reliable indices of thyroid function in this state. Although both were measured at intervals, reliance had to be placed chiefly on clinical appraisal of the patients' conditions.

In spite of these difficulties the case material is large and varied enough to warrant some tentative deductions. In most instances SPI during pregnancy in patients with thyroid disorders, as in euthyroid subjects, was greater than 6.0 γ per cent. In some instances, usually as a result of treatment, it fell below 6.0 γ per cent temporarily or did not reach this concentration until pregnancy had advanced to 16 weeks. Occasionally it declined in the terminal weeks of pregnancy. In only two patients, B90834 and C9888 (Figure 7), did it remain persistently below 6.0 γ per cent, and in these two it was above 5.0 γ per cent until 33 weeks. In general it tended to follow the course observed in normal pregnancy, rising in the course of the first 16 weeks, usually remaining elevated until delivery. The time of the initial rise varied from case to case and was frequently modified by treatment; but in cases with more than one pregnancy there was a definite tendency for the same pattern of behavior to recur despite variable treatment.

In patients with active hyperthyroidism the SPI curves tended to lie at higher concentrations than the curves of euthyroid pregnant patients. Just as the latter tolerate in pregnancy concentrations of SPI that in nonpregnant women would be indicative of hyperthyroidism, so the hyperthyroid patient appeared to tolerate still higher values without symptoms. It was not possible to demonstrate this in all the subjects because some, for example B50050, when not pregnant, on occasions had unusually high SPI without hyperthyroidism. In the hyperthyroid subjects, however, this combination occurred with far greater frequency. Only two patients, C19922 and C24644, had symptoms suggestive of persistent hyperthyroidism during pregnancy with SPI under 10 γ per cent, and in these two the signs were equivocal. This does not imply that the tolerance of the hyperthyroid to high SPI is actually greater than that of the euthyroid subject because the SPI of the latter is not easily raised to the concentrations encountered in the hyperthyroid subjects. It merely indicates that in pregnancy higher SPI can be tolerated even if this arises from overactivity of the thyroid gland. This is circumstantial evidence that the increment in pregnancy is composed of thyroid hormone. The ability of the pregnant woman to dispose of exogenous hormone was demonstrated in the preceding paper. It is also evident in the three patients whose courses are shown in Figure 7.

In those patients in which antithyroid treatment was kept unchanged or was reduced during pregnancy, the course of SPI and symptoms, especially the latter, suggest that during pregnancy the requirement for antithyroid therapy diminishes. This might be interpreted as an indication that the tolerance for thyroid hormone is increased, a view that is in keeping with the traditional concept that the activity of the thyroid gland increases during pregnancy.

A further indication that the tolerance for thyroid is increased and the need for therapy diminished during pregnancy is found in the sudden rises of SPI associated with outbursts of hyperthyroidism encountered after delivery in a large proportion of the cases, especially the flagrant outbursts

associated with high peaks of SPI. These were encountered on four occasions in nine patients with definite hyperthyroidism. The three patients in whom they occurred were all followed for long periods without other similar incidents. All the peaks were noted within the narrow interval of 10 to 12 weeks after delivery. Since they appeared to be wholly or partly self-terminative and of short duration, they might have been discovered more often if observations postpartum had been made with greater frequency. Lesser rises of SPI associated with hyperthyroidism were noted after delivery in several other instances. These rises associated with hyperthyroidism differ from the persistently high values immediately after delivery, which are symptomless. SPI does not always fall immediately after delivery in hyperthyroid patients any more than it does in normal subjects (3); but may stay elevated for some time. These elevations, like those after normal pregnancy, are not associated with signs of hyperthyroidism. The tolerance to SPI is not coterminal with pregnancy but outlasts it by an appreciable interval. Both tolerance and interval may be greater in the thyroid patient. But, if the rise persists beyond a certain time, symptoms appear. The SPI of C38870 (Figure 5), for instance, rose to 15.9 γ per cent 11 days after delivery without evidences of hyperthyroidism, but six weeks later with the same concentration of SPI she had distinct symptoms.

The tendency for SPI to rise during pregnancy was evident even in the patients with hypothyroidism. This might suggest that the high SPI signified not increased secretion and utilization, but some block to the utilization of thyroid hormone. This interpretation appears unlikely, first of all because of the tolerance for exogenous thyroid evinced by euthyroid pregnant women (3). The lesser need for antithyroid therapy would also argue against such an hypothesis, unless it be also presumed that the secretory activity of the thyroid is decreased during pregnancy, which would make it difficult to explain the high values of SPI. The rises after delivery would be equally unaccountable on this basis. It would also be necessary on the diminished utilization theory to hypothesize that the tissues required less thyroid during pregnancy, else the hypothyroid patients should have sunk into myxedema as SPI rose. The SPI of case B82863 (Figure 1) shot up with the appearance of active hyperthyroidism after propylthiouracil had been discontinued for only two weeks, descending with equal speed when the previous dose of drug had been resumed. This rapid reaction indicates that secretion, utilization and sensitivity are all active. It has been remarked that in the authentic hypothyroid, 88453 (Figure 6), the low SPI found at 15 weeks followed abstention from medication for only one week. If it be assumed that it had previously been as high as it later was on the original dose of 0.12 gm., this would suggest an unusually rapid deterioration. C18328, in the same figure, appeared to utilize increasing amounts of thyroid in the later part of pregnancy. It is probable that clinical hypothyroidism in many cases is not a total, but a partial, deficiency. In some cases, indeed, it may represent only the absence of the normal stimulus to thyroid activity. It is conceivable that the stimulus of pregnancy may break down this inhibition or arouse the residual thyroid tissue to activity. In this connection the response of C15718 (Figure 8) is most suggestive.

In the preceding paper (3) it was pointed out that the SPI's of women receiving exogenous thyroid could remain low without compromising pregnancy. In the present series persistently low SPI was encountered only in patients who were receiving exogenous thyroid.

The argument thus far has presupposed that the increment of SPI in pregnancy is of the same composition as the preexisting SPI, chiefly thyroid hormone. This presumption is open to challenge. Danowski and associates (5) found that extraction of the serum with butanol by the method of Taurog and Chaikoff (6) yielded values in pregnancy that did not differ from SPI more than the values by the two methods differed in the sera of normal individuals. Similar results have been obtained by us in a number of sera (7). In this respect, at least the increment in pregnancy behaves like thyroxine. In addition, the reaction of euthyroid pregnant women to thyroid and the behavior of the patients with thyroid disorders presented in this paper are more easily explained on the hypothesis that the increment of SPI does consist of thyroid hormone.

SUMMARY AND CONCLUSIONS

The clinical course and the SPI during pregnancies of 16 patients with disorders of thyroid function have been analyzed. Treatment was limited to the use of thiourea, propylthiouracil, Lugol's solution and dried thyroid. The hyperthyroid patients became and remained euthyroid with concentrations of SPI characteristic of normal pregnancy, distinctly above those of normal nonpregnant women. There is some evidence that they were able to tolerate in pregnancy concentrations greater than 10 γ per cent, the highest value observed in euthyroid pregnant subjects. The data suggest that the requirements for antithyroid drugs may diminish during pregnancy and increase after delivery.

The implications of these phenomena with respect to the nature and significance of the high SPI of pregnancy are discussed.

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