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SERUM PROTEIN - BOUND IODINE LEVELS IN PREGNANCY AND
THEIR SIGNIFICANCE

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PREFACE

This thesis was written in an attempt to bring into view a suggested treatment for the prevention of abortions, and an outline for the treatment of habitual abortors. It is a review of general well-known facts about serum protein-bound iodine determinations and its correlation with normal and abnormal pregnancy.

TABLE OF CONTENTS

	Page
I. Introduction	1
II. General Facts of P.B.I. and Its Determination	1
III. Serum Levels in Pregnancy	3
(a) Serum Levels in Normal Pregnancy	3
(b) Serum Levels in Abnormal Pregnancy	4
(c) Serum Levels in Abortion	5
(d) Animal Experiments with Thyroid Hormone	6
(e) Treatment of Threatened Abortion and Low P.B.I. Serum Levels	6
IV. Discussion	9
V. Summary	12
VI. Bibliography	

INTRODUCTION

In 1919 Kendall succeeded in isolating thyroxin in the blood of an ox. Since this time, many simplified procedures have been tried to measure the activity of the thyroid gland. In 1941 the separation of blood iodine into fractions was accomplished with measurements of one gamma per hundred milliliters. Present day methods are accurate to 0.2 gamma per hundred milliliters of blood. This is the measurement of protein-bound iodine, (P.B.I.).¹

The measurement of P.B.I. is one of the most accurate chemical tests of thyroid function known today. In this paper a review of the literature is made on the determination of P.B.I. with special reference to this chemical test in pregnancy.

GENERAL FACTS OF PROTEIN - BOUND IODINE AND ITS DETERMINATION

Iodine is present in the blood stream in two forms—inorganic and organic. The inorganic iodine consists of approximately ten per cent of the total iodine. There is a small amount of organic iodine not bound to protein. This is lost in the determination of P.B.I. The P.B.I. determination consists mainly of thyroxin with less than one gamma per hundred milliliter consisting of diiodothyroxine-like iodine which may include triiodothyronine.² Gross and Pitt-Rivers³ have shown in their study on rats that triiodothyronine has five times the activity of thyroxine and concluded that triiodothyronine is the peripheral thyroid hormone

and that thyroxine is its precursor.

Taurog and Chiakoff₄ have shown that the P.B.I. of rat plasma labeled with I^{131} follows thyroxine carrier quantitatively. They have also shown that thyroxine takes six hours to produce an effect when given to rats by injection.

P.B.I. is elevated in hyperthyroidism, early hepatitis, and immediately following thyroidectomy. P.B.I. is depressed in hypothyroidism, nephrosis, post-operative thyroidectomy, and Riedel's struma.₁

P.B.I. is also affected by drugs with elevation when inorganic iodine such as Lugol's solution is given. The effect of administration on the P.B.I. lasts from two to five days. Organic iodines may produce an artifactual elevation in P.B.I. for months. These include most of the dyes used in roentgenographic visualization of internal structures. Radioactive iodine also causes a transient rise in P.B.I. with a long term effect of lowering the P.B.I. Drugs which lower the P.B.I. are ACTH, cortisone, mercury, and barium salts as well as thiouracil.₁ There is also a physiologic increase in pregnancy and infancy, and a decrease in senescence in the male.₂

There are three different determinations of P.B.I. in use today. The chloric acid and distillation methods which are less used,₅ and the alkaline ash method of Barker₆ which is most frequently used. This consists of taking the protein precipitate and heating

it in an oven, and then dissolving the ash which contains the P.B.I. The resulting solution is then added to arsenous acid and the ceric ammonium sulfate is added. Decolorizing is noted and readings taken in a photometer at specific time intervals. A blank is also run for impurities. The resulting value is then read on a chart previously prepared from standards. There are several modifications of Barkers original procedure, but the basic principles are the same.^{7,8,9,10,11,12,13}

The normal P.B.I. values have a mean of 5.0 gamma per hundred milliliters with a standard deviation of 1.0 gamma. The normal range is considered to be 3.5 gamma to 8.0 gamma per hundred milliliters by most laboratories, though slight variations between laboratories do occur.^{1,2,6,13,14,15,16} Levels below 3.5 gamma are hypothyroid individuals, and those above 8.0 gamma are hyperthyroid individuals. The cholesterol determinations vary widely and are of no diagnostic importance.

SERUM LEVELS IN PREGNANCY

Serum Levels in Normal Pregnancy

One hundred forty-eight cases of normal pregnancies were found in the literature.^{12,17,18,19} The mean value of P.B.I. determinations being 7.8 ± 1.3 gamma per cent with a range of 6.2 - 11.2 gamma per cent. There was one determination in three different patients in this group below 6.0 gamma per cent, but values were

above 6.2 gamma per cent on all previous and subsequent determinations.¹⁷

There is a much greater fluctuation of P.B.I. values on subsequent determinations during pregnancy than those taken in non-pregnant females.^{17,19} Values up to 10 gamma per cent are not uncommon. The elevation P.B.I. occurs two to four weeks after conception.^{7,13} One author states that P.B.I. values are elevated as soon as the Asheim-Zondek pregnancy test becomes positive.²⁰ These elevated levels seem to drop precipitously with delivery and continues to drop until it reaches normal non-pregnant levels in two weeks.

In twenty-one patients serum thyroxin levels were measured by Taurog's method. In the normal non-pregnant female the average values being 3.7 ± 0.8 gamma per cent. In the pregnant patients the values were 5.4 ± 1.0 gamma per cent. With this the albumin fraction was 3.55 ± 0.42 and the globulin 3.20 ± 0.34 , a respective lower and higher value than the non-pregnant female.¹⁹

Serum Levels in Abnormal Pregnancy

Sixteen cases of abnormal pregnancy not involving the thyroid gland were found.^{17,20} There were twelve toxemias, two diabetics, one of which had Kimmelstiel Wilson kidneys, one diabetes insipidus, and one multiple sclerosis. In all patients but one, toxemia, P.B.I. values fell within the normal range for pregnancy. Two

pregnancies were terminated (Kimmelstiel Wilson disease and multiple sclerosis) in which the P.B.I. values fell within the characteristic manner after evacuation.

Two cases of ectopic pregnancy were reported.¹⁷ In one, three weeks after menses, the P.B.I. was 4.0 gamma per cent. In the other the P.B.I., at ten weeks after menses, was 8.3 gamma per cent. This fell to 6.8 gamma per cent thirteen days after operation.

Serum Levels in Abortion

Forty-six cases of abortions were found in the literature.^{12,17} 18,20 Of these, thirty-three, or seventy-two per cent, had P.B.I. values less than 6.0 gamma per cent, and thirteen, or twenty-eight per cent, had P.B.I. values in the normal pregnancy range. Six patients who aborted had successful second pregnancies. Two with no medication had P.B.I. values of 2.7 and 5.4 gamma per cent with their first pregnancies, while with their second pregnancies, P.B.I. values were 6.5 and 8.7 gamma per cent. Two patients were given thyroid with their second pregnancy with the P.B.I. remaining in normal pregnancy levels. Two others given thyroid medication never had P.B.I. values below 5.8 gamma per cent.¹⁷

Although there are no hyperthyroid symptoms in pregnant women whose P.B.I. values rise over the normal non-pregnant range of 8.0 gamma per cent, twelve patients were found in the literature^{12,21} definitely hyperthyroid and had values over 11.2 gamma per cent.

These patients were treated with Lugol's solution or thiourea or both. Lower doses of these drugs are required in pregnancy than in non-pregnant females. Tolerance to elevated P.B.I. values seem to out-last pregnancy only a short time. One patient with a P.B.I. of 15.9 gamma per cent eleven days after delivery had no symptoms, while six weeks later, with the same P.B.I. value, symptoms appeared. Sudden outbursts of hyperthyroid symptoms after delivery in these patients are common.

Animal Experiments with Thyroid Hormone

Chu₂ found that thyroidectomy in the rabbit at an early stage of pregnancy caused reabsorption and/or abortion of the embryos, while late in pregnancy it caused the delivery of still-born young.

Rabbits which were thyroidectomized did not become pregnant but many follicles were present in the ovary. If these follicles were caused to rupture before coitus by giving chorionic gonadotropin, the resulting embryos were reabsorbed, aborted, or there was prolonged retention of the dead fetus. If these rabbits were given desiccated thyroid after pregnancy ensued, the embryos lived longer and resulted in still-births. There was an abnormally high number of embryos present.

Rabbits which were thyroidectomized and given desiccated thyroid following the operation gave birth to viable normal litters in half of the cases.

Treatment of Threatened Abortion and Low P.B.I. Serum Levels

Winkler and others²³ compared the use of oral desiccated thyroid with the effects of intravenous thyroxine on the elevation of the basal metabolic rate (B.M.R.) in myxedematous patients. There was no response in any of the group to less than five grains of thyroid per day and only two showed an increase on this amount. Five-tenths milligrams of intravenous thyroxine given to five of the patients showed a rise of thirteen to twenty-one per cent in the B.M.R. Three of the patients were given one milligram of intravenous thyroxine. Their basal metabolic rates rose from twenty-four to twenty-nine per cent above previous values.

Danowski and others²⁴ showed that P.B.I. values in euthyroid individuals at weekly intervals did not change on one grain of thyroid per day. Fluctuation in day to day P.B.I. values did not increase during thyroid therapy. Temporary decreases in P.B.I. values were noted when three grains of thyroid per day were withdrawn.

The use of hormones correlated with P.B.I. values showed that 100,000 units of estradiol raised the P.B.I. value 1.2 gamma per cent within one week. Seventy milligrams of stibesterol raised the P.B.I. values 1.2 gamma in two days.¹²

Pregnant females seem to have the same increased tolerance for thyroid medication as do myxedematous patients. It was noted that

five grains of thyroid per day did not elevate the P.B.I. above normal pregnancy values.¹⁷ Ten patients who threatened abortion or aborted had values below 6.2 gamma per cent. One patient was placed on three grains of desiccated thyroid per day and, though her P.B.I. value rose to 7.3 gamma, she aborted. She also aborted a second pregnancy without medication with a P.B.I. value of 2.8 gamma per cent.¹²

In twenty-six cases of abortion, seven cases were given thyroid or thyroxine after bleeding began without preventing abortion.¹⁷ Of ten threatened abortions, four had values less than 6.0 gamma per cent. Oral desiccated thyroid was started immediately. One patient had a P.B.I. level of 4.8 gamma per cent at seven weeks. She was given two milligrams of thyroxine intravenously and her P.B.I. rose to 18.1 gamma per cent. She delivered a normal infant at term after which her P.B.I. value was 5.8 gamma per cent. All four patients had P.B.I. values greater than 6.0 gamma per cent on medication, and all proceeded to term.¹²

In a case report¹² one patient who was three months pregnant had a P.B.I. value of 5.8 gamma per cent. She was placed on one and one-half grains of thyroid per day. At four months she developed labor pains and began to hemorrhage. In the opinion of the attending obstetrician, this was an inevitable abortion. Her P.B.I. value was 6.6 gamma per cent at this time. She was given

two milligrams of thyroxine intravenously for two days at which time her P.B.I. value was 18.0 gamma per cent. She was then placed on three grains of desiccated oral thyroid, raised to four grains the next day. She stopped bleeding and was dismissed from the hospital on her thyroid medication. At six months her P.B.I. was 10.0 gamma per cent. At eight months her P.B.I. was 7.8 gamma per cent. She delivered a normal healthy baby at term.

Man and others¹⁷ followed one patient through three abortions. During her first pregnancy her P.B.I. at two weeks was 4.5 gamma per cent. At seven weeks it was 5.3 gamma per cent. She was given five grains oral thyroid per day but she aborted at twelve weeks. In three months she became pregnant again. At five weeks of pregnancy her P.B.I. was 4.2 gamma per cent. She was placed on four grains oral thyroid per day. At eight weeks her P.B.I. was 6.0 gamma per cent. At ten weeks she was placed on five grains of oral thyroid per day. At eighteen weeks, with a P.B.I. of 7.7 gamma per cent, she aborted. Three months later, being non-pregnant, her P.B.I. was 4.9 gamma per cent. Although this was a normal value, she was given two grains of oral thyroid per day. Two days later she menstruated, and then became pregnant for the third time following this menstrual period. At five weeks of pregnancy her P.B.I. was 3.5 gamma per cent, and she was given four grains of oral thyroid, then increased to five grains per day.

At seven weeks her P.B.I. was 9.2 gamma per cent. At sixteen weeks she had uterine contractions and was placed on seven grains of thyroid per day. At twenty-three weeks of pregnancy she aborted.

DISCUSSION

It has been shown that in pregnancy there is a physiological increase in P.B.I. values that are necessary for the continuation of that pregnancy. Only three single P.B.I. values being below 6.0 gamma per cent which were above this figure on all other determinations in these pregnancies. Below this level all patients either threatened abortion or aborted.

Patients do show signs of hyperthyroidism during pregnancy, however, their P.B.I. values are above 11.2 gamma per cent. These can be treated in the conventional manner. However, smaller doses of antithyroid drugs are required than in the non-pregnant female.

Pregnancies which are abnormal from other than thyroid disorders, such as toxemia, usually have P.B.I. values in the normal pregnancy range. Ectopic pregnancies show an increase in P.B.I. values to normal pregnancy levels, with a precipitous drop when pregnancy is terminated.

Danowski²⁵ showed P.B.I. values in newborn infants up to twelve hours old are of the same order of the mother, being 8.3 ± 2.4 gamma per cent. At one week of age the P.B.I. rises to

10.9 - 1.8 gamma per cent. At one year of age their P.B.I. values are 6.3 - 1.0. These decrease until reaching the adult level of 5.4 - 0.7 gamma per cent.¹⁰ We can postulate from this that high P.B.I. values are necessary in the newborn period, therefore, necessary during early embryonic life which must be produced by the mother at this time. Low P.B.I. values in pregnancy after sixteen weeks does not increase the incidence of abortion.

In the administration of oral desiccated thyroid, it has been shown that in hypothyroid individuals and in pregnant females there is a high tolerance to the drug. Dosages above five grains per day are required to elevate the B.M.R. and P.B.I. Intravenous thyroxine, however, gives a strong immediate rise, and in two cases seemed to prevent abortions. The statistics may be clouded by the fact that threatened abortions on admission to a hospital may already be incomplete abortions. The following is a suggested outline in the treatment of low P.B.I. values during pregnancy.

Oral thyroid should be given to all pregnant patients whose P.B.I. values on two determinations are below 6.0 gamma per cent. Large doses in the range of five to eight grains should be used in view of the unusual tolerance to this drug in the pregnant female. Patients who are threatening to abort should be given two milligrams of intravenous thyroxine. Cases of habitual abortion with

low P.B.I. values in previous pregnancies should be placed on moderate doses (three to five grains per day) of oral thyroid even though their P.B.I. values fall within the normal non-pregnant range. After pregnancy ensues, routine bi-weekly P.B.I. tests should be done for the first twenty weeks, and the dosage of thyroid raised from five to eight grains per day. If at any time the P.B.I. values fall below 6.0 gamma per cent during the first twenty weeks of pregnancy, one milliliter of intravenous thyroxine should be given. If cramping or spotting ensues, two milligrams of intravenous thyroxine should be given.

SUMMARY

1. P.B.I. determinations show a physiologic elevation in pregnancy.
2. This elevation of P.B.I. values is necessary for the normal development of the embryo.
3. Pregnant females show an increased tolerance to orally administered thyroid.
4. Administration of oral thyroid to raise P.B.I. values must be given in large doses.
5. Threatened abortions and abortions are most frequent with a P.B.I. value of less than 6.0 gamma per cent.
6. Raising the P.B.I. value above 6.0 per cent by medication does not insure against abortion.
7. Raising P.B.I. values above 6.0 gamma per cent by medication decreases the number of abortions.

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