1956

Hyperthyroidism complicating pregnancy

Arnold W. Siemsen
University of Nebraska Medical Center

HYPERTHYROIDISM COMPLICATING PREGNANCY

Arnold William Siemsen

Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 2, 1956

Omaha, Nebraska

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 1

THE PROBLEM AND ITS INCIDENCE

For many years a difference of opinion has existed regarding the relative effectiveness of the different forms of treatment in hyperthyroidism complicating pregnancy. The majority of the reports made by the different proponents have been based by necessity on a limited number of observations. In Table I are tabulated 415,613 pregnancies reported in the literature of which 237 (0.057%) had been complicated by hyperthyroidism. The incidence in this series ranges from 3.7% in endemic goiter areas to 0.03% in nonendemic regions. The relative rarity of the two conditions existing simultaneously has been attributed to the sterility which is generally induced by the hyperthyroidism (35, 76, 113, 145, 167). Another factor is that hyperthyroidism has its peak incidence in the latter part of the reproductive cycle (9, 67, 74, 79, 95, 129).

In Table II are listed a series of 38,825 thyroidectomies reported in the literature of which 288 (0.74%) were in pregnant patients. The incidence ranged from 3.2% in goiter belts to 0.2% on the sea coast. By comparing Tables I and II one will note

TABLE 1

THE INCIDENCE OF HYPERTHYROIDISM IN PREGNANCY

Author	Year	Location	No. of Pregnancies	No. with Hyperthyroidism	Incidence
Halliday-Croom (140)	1903	England	15,000	1	.007%
Bonnaire(127)	1910	France	30,000	2	.007%
Markoe (155)	1918	N. Y.	100,000	8	.008%
Yoakam (116)	1928	Mich.	937	35	3.7 %
Wallace (113)	1933	N. Y.	11,571	4	.03 %
Bustos Moron (84)	1935	Argentina	30,000	5	.016%
Portis & Roth (101)	1939	Ill.	1,000	14	1.4 %
Javert (87)	1940	N. Y.	23,000	18	.076%
Baumgartner (9)	1942	Calif.	39,419	22	.06%
McLaughlin & McGoogan(129)	1943	Nebr.	6,112	19	.3 %
Davis (74)	1944	Md.	20,000	8	.04 %
Kibel (90)	1944	N. Y.	15,846	12	.075%
Whitelaw (55)	1947	N. Y.	13,264	8	.06 %
Wernicke(114)	1948	Argentina	87,415	42	.048%
Ciulla (68)	1949	Italy	10,202	18	.176%
Dailey & Benson (84)	1951	Calif.	11,390	21	.175%
TOTAL			415,613	237	.057%

TABLE II

THE INCIDENCE OF PREGNANCY IN HYPERTHYROIDISM

Author	Year	Location	Series of Thyroid-ectomies	No. of Pregnant Patients	Incidence
Mussey, et al. (95)	1926	Minn.	7,228	42	.6 %
Clute & Daniels (69)	1930	Mass.	3,678	18	.41%
Frazier & Ulrich (85)	1932	Penn.	1,350	44	3.2 %
Lehman (92)	1933	Ohio	3,350	33	1. %
Bram (128)	1936	Penn.	4,000	12	.3 %
Portis & Roth (101)	1939	Ill.	500	2	.4 %
Norrman(168)	1943	Sweden	3,000	9	.3 %
Brandes (67)	1948	Minn.	12,796	94	.7 %
Ficarra (26)	1951	N. Y.	200	4	.2 %
Bartels (180)	1952	Mass.	2,400	27	1.1 %
Sirven (50)	1952	Argentina	318	3	.94%
TOTAL			38,825	288	0.74%

that the incidence of pregnancy in established thyroid disease is over ten times as high as the incidence of thyroid disease developing during pregnancy.

We can conclude, therefore, that hyperthyroidism complicating pregnancy is relatively rare. Nevertheless, the problem is important and indeed difficult, for upon its adequate solution depends the life of both the mother and the baby.

CHAPTER II

DIAGNOSIS AND COURSE OF UNTREATED CASES

Women with a normal functioning thyroid on becoming pregnant may give evidence of a mild hyperthyroidism (24, 60, 85, 113, 134). These symptoms are nervousness, insomnia, headache, palpitation, elevated blood pressure, tachycardia, tremor, nausea, vomiting, sweating, weight loss, enlargement of the thyroid gland and sometimes slight exophthalmos. Thus, some writers call pregnancy a "hyperthyroid state." (79, 238)

Bothe (13) observed that in a high percentage of patients, who had hyperthyroidism complicating pregnancy, there was a history of prolonged nausea and vomiting during previous gestations. Hyperemesis is a common symptom of hyperthyroidism but responds on treatment with Lugol's solution and thus can be differentiated from hyperemesis gravidarum (67).

Hypertrophy of the thyroid gland during pregnancy was known to the Romans (24) and has been reported frequently since that time (25, 26, 35, 60, 67, 70, 73,74, 75, 97, 104, 107, 116, 121, 134, 145, 149, 152, 164, 167, 196, 197, 198, 199, 200, 201, 202). The incidence of enlargement of this gland has been reported as ranging from 31% to 90% (23, 26, 35, 67, 73, 74, 75, 83, 90, 101,

104, 110, 111, 143, 145, 157, 198, 199). The higher percentages are found in endemic goiter areas, in older women, in patients with large families and in those who have had several children in rapid succession. The lower percentages are found in nonendemic regions.

The increase in the size of the thyroid gland first appears around four to five months in multiparas and about the sixth month in primigravidas (74, 110). It decreases in size after delivery (14, 21, 24, 25, 74, 110, 138, 140, 149, 237, 250), but involution after termination of the pregnancy is never complete and the gland tends to get larger with each successive pregnancy (75, 83, 143).

Crotti (70) in 1917 stated that the thyroid hyperplasia is a physiological process with a purpose of ridding the body of waste products. Hinton (75), on the other hand, considers it more of a pathological process secondary to increased demands on the body. To help them in deciding between the two types, Crotti (71) and Bram (128) use the criteria of expected weight gain and basal metabolic rate (BMR). The thyroid enlargement is secondary to an elevated thyrotropin concentration (126, 156). As a result of hyperactivity of this gland, there are changes in the: a. blood iodine; b. iodine content of the thyroid gland; c. distribution of calcium; d. BMR; e. plasma cholesterol; f. serum precipitable iodine (SPI); g. liver glycogen; h. ketone

bodies in the urine and blood; i. insulin effect; j. adrenal secretion. The degree of hyperactivity is reflected in the magnitude of these changes.

It is generally considered that the average normal blood iodine level in nonpregnant women is 11.0 micrograms percent (166, 203). Pregnancy causes an increase in this value (63, 126, 145, 166, 203, 205, 230). The increase is all or nearly all in the protein-bound fraction of the blood (63, 230). Bokelman and Scheringer (126) observed a blood iodine value of 15.5 micrograms percent at two months which increased to 24.9 micrograms percent at nine months of gestation and then dropped to 17.7 micrograms percent by two weeks following delivery. Similar findings were observed by Stepto (110) and Zener, et al. (166). There is a corresponding decrease in the iodine content of the thyroid gland from a normal value of 0.2% to 0.1% (110).

With increased thyroid activity there is mobilization of calcium from the maternal bone. The embryo needs this calcium for developing new osseous structures. The thyroid apparently makes this element preferentially available to the developing fetus (145).

Magnus-Levy (223) in 1897 described the increased BMR observed in pregnancy. This was later varified by additional workers in the field (63, 73, 79,

95, 104, 134, 163, 166, 196, 204, 205, 207, 210, 211, 212, 217, 220, 222, 230). The elevation of the BMR has been attributed to the increased fetal and maternal protoplasmic mass (95, 208, 209, 210, 212, 214, 219, 221, 225). Some authors disagree with this finding and feel that there is an increase beyond this amount for which they can offer no explanation (215, 217, 224). The onset of the increased BMR varies from author to author. Wilson (167), Root and Root (211), Mangus-Levy (216) and Hughes (217) report that the BMR starts to increase at the third or fourth month, Hanna (219) at the fifth month, Rowe and Boyd (224) at the sixth month and Sandiford and Wheeler at the eighth month. Root and Root (211), Hughes (217) and Rowe and Boyd (224) report subnormal BMR values for their patients prior to the third or fourth month. What then is a normal increase in the BMR and above what value would it be significant? The upper limits of normal which have appeared in the literature are listed in Table III. They range from 2.4% to 35%. As is generally known, this method has many sources of error (116, 220) and on this basis would explain some difference in the values reported. Also, the technique has gradually become more and more improved over the years.

The BMR usually returns to normal within fourteen days after delivery of the fetus. (74, 128, 167,

TABLE III

THE NORMAL INCREASE IN THE BMR IN PREGNANCY

BMR	Source
2.4%	Davis (73) 1926
4.0%	Zuntz (204) 1910 Hasselbach (218) 1912 Carpenter & Murlin (221) 1911
4.5%	Stander & Peckham (208) 1926
5.0%	Ficarra (26) 1951
13.0%	Rowe & Boyd (224) 1932
14-16%	Hanna (219) 1938
15-20%	Plass & Yoakum (213) 1930 Jond ahl, Banner & Howell (89) 1949 Sirven & Navarret (50) 1952
20-25%	Mussey, Plummer & Boothby (95) 1926 Sandifor, Wheeler & Boothby (209) 1931 McGavack (145) 1951
25-30%	Clute & Daniels (69) 1930 Davis (74) 1944 Wilson (167) 1930 Falls (79) 1929
20-35%	Bram (128) 1936
33-35%	Baer (222) 1921

208, 210, 219,222). These authors consider it abnormal if the BMR remains elevated after this time. Zener, et al. (166) allow the BMR six weeks to return to normal. There is some elevation of the BMR associated with lactation (215, 221). This value, however, should not exceed one-half of the value obtained prior to labor. Phatak, et al. (203) in 1940 found that if they gave iodine during pregnancy the BMR stayed close to normal. Their patients required more during the third trimester.

Gardner and Gainsborough (226) found the free cholesterol of the plasma to increase to a maximum at the thirtieth week. Concurrently they observed a decrease in the ester cholesterol to a minimum at about the same time. From the thirtieth week on to term the free cholesterol decreased and the ester fraction rose until a normal ratio was attained. They found less definite changes in the total although some showed an increase. Boyd (227) observed an 8% increase in the total cholesterol at term over the non-pregnant state. The esters were up 14% and the free were little altered.

In 1931 Anselmino and Hoffman (228) demonstrated a substance in the blood which had all of the properties of thyroxine. It was present throughout pregnancy and reached its maximum at term, falling rapidly in the puerperum to a normal level by the sixth day. The

concentration was much lower in the fetal circulation than in the maternal circulation and at times could not be demonstrated at all.

Man, et al. (229) in 1942 investigated the serum precipitable iodine (SPI). They found this fraction to contain at least 80% diiodotyrosine iodine and virtually all of the iodine in thyroxine. Heinemann, et al. (63), Peter, et al. (230), Man, et al. (231), and Engstrom, et al. (232) felt the SPI was a more accurate measurement of circulating thyroxine then the BMR. Their normal values for the pregnant woman were 6.1-11.2 micrograms percent and for the non-pregnant woman 4.0-8.0 micrograms percent. A physiological increase in this value was noted as early as three to six weeks after conception and did not subsequently change during the gestation. This value returned to normal after delivery. Therefore, the SPI curve does not correlate with the BMR. And, finally, it has been reported by Dailey and Benson (84), Jondahl, et al. (89) and McGavack (145) that the thyroid hyperactivity is the cause of a dimunition of liver glycogen, an increase of ketone bodies in the blood and urine, over secretion of adrenalin and a decreased insulin effect.

Diffuse goiter with hyperthyroidism, also referred to as Graves' disease, Basedow's disease or

exophthalmic goiter frequently first manifests itself during or just following pregnancy (25). Falls (25) states that it is not hard to conceive the possibility of a gland which may or may not have a preceeding tendency to develop a toxic goiter which under the stress of pregnancy with stimulation and alteration of the function of all ductless glands and the sympathetic nervous system becomes toxic.

Graves' disease is generally characterized by an acute onset of toxic symptoms particularly during the first four months of pregnancy (15, 86, 167). Jackson (86) states that the average duration from the time the goiter is first noticed until toxic reactions occur is generally nine months while Brandes (67) feels that they usually occur simultaneously. The disease proceeds in waves with definite periods of remissions (86) thus accounting for the fact that some women can get pregnant (113, 239, 241). As opposed to adenomatous goiter, Graves' disease appears to cause a more rapid and severe weight loss (86). The average age of patients with diffuse goiter in pregnancy has been reported as 27 years by McLaughlin and McGoogan (129), 27.3 years by Brandes (67), 29 years by Baumgartner (9), 30 years by Falls (79) and 34 years by Davis (74). As can be told from Table IV exophthalmic goiter occurs three times more frequently in

TABLE IV

INCIDENCE OF DIFFERENT TYPES OF GOITER IN PREGNANCY

No. of pts. with Nodular Goiter	No. of pts with Diffuse Goiter	Source
9	7	Watson (165) 1918
10	32	Mussey (95) 1926
8	10	Falls (79) 1929
887	2791	Clute, et al. (69) 1930
3	11	Fahrni (78) 1930
2	13	Lahey (91) 1931
21	23	Frazier, et al. (85) 1932
26	57	Mussey (156) 1938
5	17	Baumgartner (9) 1942
34	41	Brandes (67) 1948
TOTAL: 1,005	3,002	
INCIDENCE: 25%	75%	

pregnancy than adenomatous goiter. The apparent explanation is the fact that Graves' disease occurs at a younger age than nodular goiter.

Nodular or adenomatous goiter with hyperthyroidism is generally characterized by a more gradual onset of toxic symptoms (25, 75) and is considered less dangerous than Graves' disease by Jackson (86) and Wilson (167). McLaughlin and McGoogan (129) consider adanomatous goiter more serious and report two maternal deaths from this type. Wallace (113), Bothe (13) and Bram (14) point out that the danger from nodular goiter is probably less from the toxemia itself than from the strain of pregnancy, labor and delivery imposed upon organs already damaged by a long continued thyroid toxemia. The heart complications tend toward arrhythmias (86, 167). Kidney (86) and liver damage (245) have also been reported. The average duration between the onset of the nodular goiter and the development of toxicity has been reported as 11.3 years by Brandes (67) and 16-18 years by Jackson (86) and Mussey (156).

Patients with adenomatous goiter may remain symptom free even with pregnancy (156, 167) or as is even more common they may get pregnant while hyperfunctioning (156). The average age of women

who are pregnant and have adenomatous goiters has been variously reported as 31 years by Falls (79), 32 years by McLaughlin and McGoogan (129), 33 years by Baumgartner (9), 34.8 years by Brandes (67) and 44 years by Jackson (86). Mussey, et al. (95) report that 70% of their patients with this type of goiter were over 40 years of age.

The BMR in nodular goiter is less than that obtained in exopthalmic goiter (25, 86). In a series of seventy-five patients at the Mayo Clinic (67) the average BMR of patients having toxic diffuse goiters was 42.3% and of those have toxic nodular goiter, 33.4%. Adenomatous goiter patients seem to have a greater power of recovery and less danger of subsequent recurrence with succeeding pregnancies than in Graves' disease (167). The danger of tracheal compression is always present and is usually seen more often in nodular goiter (25, 91).

Many authors feel hyperthyroidism is aggravated by pregnancy (8, 14, 21, 30, 45, 70, 71, 76, 78, 97, 106, 128, 129, 136, 137, 139, 150, 161, 170, 242, 248, 250, 252), while others think the disease is aided by pregnancy (4, 15, 87, 90, 103, 122, 135, 138, 154, 233, 241). Still other investigators feel that pregnancy in the majority of cases did not alter the course of hyperthyroidism (21, 59,

67, 79, 84, 93, 95, 103, 138, 164). The improvement associated with becoming pregnant has been explained by a decrease in the concentration of thyroxine in the circulating blood secondary to the increased demands of the new organism for this substance. (130, 246).

Some authors feel that the placenta is permeable to thyrotropin (27, 35, 143, 185), others deny this statement (187, 188, 190, 194). The majority of the writers in the literature believe the placenta is permeable to thyroxine (15, 27, 130, 148, 193, 194). There is only one conflicting view (192).

There are reports in the literature which state that in the hyperthyroid state there is an increased incidence of toxemia of pregnancy (21, 48, 50, 86, 87, 90, 121, 129) while still other authors find no relationship (67, 84, 149, 239). Toxemia of pregnancy has been reported to result from failure of the thyroid gland to hypertrophy (73, 246, 249), untreated or inadequately treated hyperthyroidism (59, 62) and an elevation in the end products of metabolism secondary to toxic diffuse or nodular goiter (99).

Untreated hyperthyroidism complicating pregnancy causes an increase incidence of spontaneous

abortions (14, 15, 17, 35, 50, 59, 62, 67, 68, 84, 97, 98, 103, 105, 106, 121, 125, 138, 141, 241) and premature deliveries (59, 67, 74, 106, 121, 138, 161, 239) and a secondary elevated fetal mortality rate (4, 106, 138). All other things being equal, woman who miscarry, having hyperthyroidism are worse off than those who go to term (14, 128, 138). There are apparently two reasons: a. the unhappy mental status of the mother on losing her baby and b. the disturbances of the endocrine glands especially the sex organs and the thyroid gland. These authors feel it is much easier to manage a patient who has gone to term than one who has aborted. Halliday-Croom (141) found that Graves' disease was temporarily made worse by the onset of labor.

In the management of labor in patients having hyperthyroidism the following five principles should be considered: a. The patient should not be allowed to strain with contractions (89) as there is danger of precipitating congestive heart failure, (74, 138, 167), increasing vascularity and size of the thyroid (74, 116, 138) and causing blood extravasation into the thyroid tissues (167); b. Pain should be avoided (74, 109, 128) as it may cause shock; c. The second stage of labor should be short-

ened (89, 112); d. The patient should be observed for postpartum hemorrage as there is a decreased clotting time (86, 89, 105, 128, 141, 151, 154, 158, 167, 239, 241, 247); e. These deliveries are characterized by vigor and violence with sebsequent birth injuries to both mother and child (167). Rutherford (237) along with Dailey and Benson (84) relate that the fetus is usually normal and healthy. There was an increase in the placental weight in those patients delivered by Follmer (80). Bothe (60) suggests that these patients be followed closely at two week intervals for some time after delivery as the symptoms may not be relieved. Bram (128) feels that these patients should not become pregnant for at least six months following their last delivery.

CHAPTER III

A GENERAL CONSIDERATION OF THE ANTITHYROID COMPOUNDS

Astwood (118) in 1943 reported the first clinical use of thiouracil in the control of hyperthyroidism. Good and unfavorable results soon appeared in the literature. The adverse effect on adults consisted primarily of hyperplasia of the thyroid gland resulting in mechanical compression of structures in the neck (117, 124, 175, 171, 133), an increased exophthalmos (171, 133), formation of adenomata in rats after prolonged administration (176) and toxic and hypersensitive reactions. The incidence of the toxic and hypersensitive reactions with thiouracil was reported as 10% by Astwood (5) in 1944, 11.5% by McGavack (38) in 1944, 21.6% by Rose and McConnell (172) in 1944, 14.5% by Williams, et al. (175) in 1946 and as 11% by Heyd (81) in 1946. The most common reactions as reported by these authors were granulocytopenia, leukopenia, fever and skin eruptions. Their lists also included: diarrhea, hematuria, anemia, jaundice, pharyngitis, myalgia, arthralgia, anorexia, chills, nausea, vomiting, enlargement of the submaxillary gland, headache, purpura, lymphadenopathy, oral sepsis and psychosis.

Nevertheless, the drug was effective in

controlling the symptoms of hyperthyroidism in a high percentage of cases (62, 172, 174, 178), and in giving a high incidence of lasting remissions (62). Van Winkle, et al. (174) in 1946 sent 5,745 questionnaires to 328 investigators regarding the use of thiouracil. Of this group 75% felt the incidence of adverse reactions to this medication was less than the incidence of complications from current methods of treatment. Thiouracil was, therefore, a step forward in the medical management of hyperthyroidism.

The search for a less toxic compound continued and in 1946 Astwood (6) reported that propyl-thiouracil had fewer side effects than the other goitrogens. The fact that this drug did give toxic reactions as pointed out in 1948 by Curtis and Swenson (133) could not be overlooked. In 1952 Bartels (180) observed that 1.6% of his patients had significant toxic manifestations which were predominately agranulocytosis, leukopenia and fever. He found agranulocytosis in 1% of his patients. Four deaths attributed to propyl-thiouracil induced agranulocytosis are reported in the literature (181, 182, 183, 184).

More compounds were tried and in 1949 Stanley and Astwood (177) studied the relative activities of the antithyroid drugs. Arbitrarily giving thiouracil

the value of 1.0, they found that propylthiouracil would then have an activity of 0.75, Methylthiouracil 2, mercaptoimidazole 10, and methylmercaptoimidazole 100. Bartels (180) feels that methylmercaptoimdazole is only ten times more active than propylthiouracil.

In 1952 Bartels (180) reported the use of tapazole (methylmercaptoimidazole) in two hundred and fourteen patients. He observed toxic reactions in 7.5% of his series. Skin manifestations made up the largest number. Granulocytopenia and arthralgic pains were also noted. He was able to find one case of nonfatal agranulocytosis and one case of granulocytopenia in the literature. He knows of two fatalities attributed to agranulocytosis. Patients who did not tolerate the drug were switched to propylthiouracil. In some cases a reduced dose with or without pyribenzamine would stop the adverse response to the medication.

Propylthiouracil and tapazole have been uniformly effective in controlling hyperthyroidism with only a few exceptions (179, 180). Higher doses are usually required for large nodular goiters associated with severe hyperthyroidism (5). The dose generally recommended for propylthiouracil varies from 0.3-0.9 grams daily with a maintainance of 0.05-0.2 grams per day (179) to 0.4 grams daily. It is given in 3-6 divided doses.

The dose of tapazole varies from 0.015-0.6 grams per day with a maintainance of 0.015-0.005 grams per day (179) to 0.02-0.04 grams daily (180). This drug is also given in 3-6 divided doses.

Bartels (180) had little preference between propylthiouracil and tapazole. The reactions were few, but nevertheless the patient must be followed closely for fever, sore throat, skin reactions, leucopenia, granulocytopenia, etc. (11, 145, 180). Bartels (180) feels that a white blood cell count and a differential should be done before therapy is started and then weekly for three to four weeks. The drugs should probably be discontinued if: a. there is a leucocytopenia of 3,000 or less with a normal differential, b. there is a leucocytopenia of 3,500 or less and a granulocytopenia of 35% or less or c. there is a normal leucocyte count but a granulocytopenia of 25% or less.

CHAPTER IV

THE INFLUENCE OF THIOURACIL, METHYLTHIOURACIL, PROPYLTHIOURACIL, MERCAPTOIMIDAZOLE AND METHYLMERCAPTOIMIDAZOLE ON THE PREGNANT PATIENT.

In the preceeding chapter, I have discussed some of the general features of thiouracil, methylthiouracil, propylthiouracil, mercaptoimidazole and methylmercaptoimidazole. This chapter will deal primarily with the aspects peculiar to the gravid state.

Bissell (11) in 1945 wrote, "The avoidance of surgery during pregnancy whenever possible is generally practiced. This would seem to apply to thyroidectomy." Thus, he and others (4, 6, 62, 68, 99) favor the use of these drugs in pregnancy. They feel that in a large percentage of the cases the pregnancy will be allowed to carry through to term.

In table V I have collected a list of hyperthyroid pregnant women from the literature who were treated with these drugs. No adverse effects were noted on the mother in this group. This series consists of one hundred and twenty-five patients of which fifty received thiouracil, eighteen methylthiouracil, forty-five propylthiouracil, one mercaptoimidazole and eleven methylmercaptoimidazole. All daily doses were given in three to six divided amounts.

TABLE V

MOTHERS RECEIVING ANTITHYROID THERAPY WITHOUT ADVERSE REACTIONS

No. of cases	Medication	Source
1	Thiouracil last 4 mons. If BMR greater than 50 %: .8-1.0 gm./day for 5-10 days. If BMR 30-50%: .6 gm./day. If less then 30%: .4 gm./day with a maintenance of .2 gm./day or less.	McGavack, et al. (38) 1944
1	Thiouracil .6 gm./day for 4 mon., .4 g. per day for 1 mon., then .2 gm./day for 3 mon.	Eaton (20) 1945
3	Thiouracil .1 gm./day for 3 days, .6 gm./ day for 3-6 days, .4-.5 gm./ day until improvement. Maintenance dose was .1-.3 gm./day.	Palmer (41) 1945.
1	Thiouracil .5-.6 gm./day for 2 wks., .3-.4 gm./day until BMR normal. .2 gm. per day after 2-3 mon. Maintenance dose of .1 gm./day. Treated 1st 8 mon.	Williams and Clute (64) 1945
2	Thiouracil .5-.6 gm./day for 2 wks. .3-.4 gm./d ay for 2 wks. Treated last mon. of pregnancy.	Williams & Clute (64) 1945
2	Thiouracil (One pt. maintained on .15 gm./day.)	Sexton (49) 1946
1	Thiouracil .6 gm./day for 4 wks., .4 gm./day for 4 wks.	Strouse & Drabkin (51) 1946
3	Thiouracil given throughout pregnancy. (one pt. received .2 gm./day for last 3 mon.)	Williams, et al, (56) 1947
9	Thiouracil for one mon. or longer during pregnancy.	Williams, et al, (56) 1947
1	Thiouracil .1 gm./day for first two and one-fifth mon. of pregnancy.	Acton & Cottrell (3) 1949
3	Thiouracil	Verel (53) 1949
4	Thiouracil	Trotter (52) 1951
18	Thiouracil: 12 pts. for a long time, 6 pts. for a short time.	Keynes (35) 1952
1	Thiouracil .6 gm./day from the 3-5th mon.	Sirven & Navarret (50) 1952

TABLE V CONTINUED

MOTHERS RECEIVING ANTITHYROID THERAPY WITHOUT ADVERSE REACTIONS

No. of cases	Medication	Source
1	Methylthiouracil throughout 1st part of pregnancy	Freiesleben & Kjerulf-Jensen (27) 1946
1	Methylthiouracil for 4 months.	Vogt (54) 1946
1	Methylthiouracil .2-.3 gm./day for 9 mon.	Frisk (28) 1947
1	Methylthiouracil .6 gm./day for 3 wks., .1 gm./day for 5 wks, nothing for 4 mon. and then .1 gm./day for 1 mon.	Ball & Morrison (8) 1948
1	Methylthiouracil .2 gm./day for 4 mon., .1 gm./day for last 3 mon.	Hone & Magarey (31) 1948
1	Methylthiouracil .2 gm./day for 5 mon.	Morris (40) 1953
11	Methylthiouracil .4-.5 gm./day. Stopped 2 mon. before EDC.	Piper & Rosen (42) 1954
1	Methylthiouracil .1 gm./day for 9 mon.	Marussi-Scarizza (39) 1954
1	Propylthiouracil .15 gm./day plus 10 gtts. of Lugol's t.i.d. for 2 mon.	Bain (7) 1947
1	Propylthiouracil	Reveno (43) 1948
1	Thiouracil for 2 mon. and propyl-thiouracil for 7 mon.	Reveno (43) 1948
1	Thiouracil .6 gm./day for 5 wks. then propylthiouracil .15 gm./day for 4 3/4 mon.	Caren (15) 1949
1	Propylthiouracil .15 gm./day for 2 mon. then 0.075 gm./day for 5 mon.	Ryan & Kooperstein (45) 1949
1	Propylthiouracil .3 gm./day for last mon. with addition of Lugol's 10 gtts. t.i.d. from 36th to 39th week.	Eisenberg (21) 1950
1	Propylthiouracil .075 gm./day for 2 wk. then .15 gm./day for 2 wks., .25 gm./day for 2 wks, .15 gm./day for 3 wks, .2 gm./day for 2 mon.	Saslow & Kroff (45) 1950

TABLE V CONTINUED

MOTHERS RECEIVING ANTITHYROID THERAPY WITHOUT ADVERSE REACTIONS

No. of cases	Medication	Source
1	Propylthiouracil .1-.2 gm./day for last 6½ mon. Lugol's 10 gtts. t.i.d. added last mon.	Seligman & Pescovitz (47) 1950
13	Propylthiouracil .3 gm./day until euthyroid then .15 gm./day. Started during or shortly before pregnancy.	Astwood (4) 1951
1	Propylthiouracil .25 gm./day for 9 mon.	Hepner (30) 1952
1	Propylthiouracil .1 gm./day plus 10 gtts. of Lugol's t.i.d. for 5 mon.	Saye, et al. (46) 1952
2	Propylthiouracil .15-.2 gm./day gradually decreasing to .05 gm./day. Given for last mon.	Seligman (48) 1952
3	Propylthiouracil .15-.2 gm./day gradually decreasing to .05 gm./day. Given only during first trimester.	Seligman (48) 1952
1	Propylthiouracil .3 gm./day. Stopped two months prior to E.D.C.	Piper & Rosen (42) 1954
15	Propylthiouracil and Tapazole using 2/3 usual dose of one of these drugs plus 5 gtts. of KI daily.	Williams (58) 1955
1	Mercaptoimidazole .1 gm./day decreased with clinical response.	Astwood (4) 1951
2	Methylmercaptoimidazole .015 gm./d ay	Astwood (4) 1951
3	Propylthiouracil .3 gm./day until euthyroid, then .15 gm./day for a short time. Then changed to .015 gm./day of methylmercaptoimidazole.	Astwood (4) 1951
6	Methylmercaptoimidazole .015 gm./day. Stopped treatment two months prior to E.D.C.	Piper & Rosen (42) 1954

The largest amount of thiouracil apparently was that used by Eaton (20) which consisted of 0.6 gm./day for four months, 0.4 gm./day for one month and finally 0.2 gm./day for the last three months. Palmer (41) in 1945 and Williams (57) in 1946 gave desicated thyroid in amounts of 0.120 gm./day and 0.064-0.096 gm./day, respectively, in addition to the antithyroid compounds. This was used to decrease the eye signs and the size of the goiter. It was found not to interfer with the thiouracil. Of the fifty mothers receiving thiouracil, mention of relapses is made in only three cases (3, 53).

The largest quantity of methiothiouracil employed was that of 0.2-0.3 gm./day for nine months by Frisk (28). Aaron (1) reports the largest amount of propyl-thiouracil which was 0.3 gm./day for nine months. Only one patient received mercaptoimidazole and that was given in a dose of 0.1 gm./day decreasing with clinical responce. Nine patients received 0.015 gm. of methyl-mercaptoimidazole per day.

In table VI I have collected five cases from the literature in which adverse conditions resulted in the hyperthyroid pregnant patient. These adverse reactions all occured with thiouracil and methylthiouracil. Two deaths are reported.

Seligman (48) feels that the antithyroid therapy

TABLE VI

MOTHERS RECEIVING ANTITHYROID THERAPY WITH ADVERSE REACTIONS

No. of Cases	Medication	Source
1	Thiouracil .2 gm./day. Mother died suddenly	Davis & Forbes (19) 1945
1	Thiouracil .6 gm./day for 1 mon. .4 gm./day for 3 mon. Stopped for 1 mon. NaI: 2 minims/day for 18 days. Thiouracil .6 gm./day for 13 days, 1.2 gm./day for 1 wk. Pt. developed agranulocytosis 1 mon. post partum and died 13 days later of a thyroid crisis.	Carns & Poser (16) 1946
1	Thiouracil .6 gm./day for 2 mon. .1 gm./day for 1 mon. .6 gm./day for 1 mon. Fever and conjunctivitis developed. Pt had thyroidectomy 4 wks. postpartum.	King & Collen (36) 1947
1	Thiouracil .6 gm./day for 1 mon. .1-.2 gm./day for 4 mon. .4-.6 gm./day for the last 3 mon. Pt developed leucopenia.	King & Collen (36) 1947
1	Methylthiouracil .2 gm./day for the last 4½ mon. Mother was myxedematous on the 13th postpartum day.	Elphinstone (22) 1953

in the latter months of pregnancy is not as effective as earlier in the gestation. Bell (59) observed this same fact. Seligman feels that this may be due to the fact that the endocrine and neuropsychiatric balance of the pregnant women becomes more unstable in the last two months prior to term.

Greenhill (62) in 1955 observed that drugs like propylthiouracil and methylmercaptoimidazole could be used if only employed to bring the patient to a "pregnant euthyroid" level. He recommends 0.3 gm. of propylthiouracil every day until the symptoms are controlled and then 0.15 grams per day. He gradually decreases the amount if possible during the latter month of pregnancy. He employs a dose of 0.03 gm. of methylmercaptoimidazole daily and then reduces this to 0.015 gm./day after the hyperthyroidism is well controlled. Williams (58) writing in this same year recommends two-thirds of the usual dose of these two drugs plus five drops of KI daily.

CHAPTER V

THE INFLUENCE OF THIOURACIL, METHYLTHIOURACIL, PROPYL-THIOURACIL, MERCAPTOIMIDAZOLE AND METHYLMERCAPTO-IMIDAZOLE ON THE INFANT

In a discussion of this type it readily becomes apparent that the physician must not only consider the influence of his medication on the mother but also on the baby both during and after the termination of her pregnancy. Table VII summarizes the fetal abnormalities reported in the literature which have been attributed to the thiouracil derivatives. This series consists of twenty-one infants including one set of twins. It is obvious that the two conditions reported most frequently are those of simple thyroid enlargement and cretinism. Only one other type is mentioned and that is a case of an anacephalic monster with a cleft palate.

Nine patients were treated with thiouracil. The highest dose was 0.2-0.6 grams per day during the entire pregnancy. There were no infantile deaths. Of those babies having abnormalities at birth, all recovered within a short period of time. There was no permanent impairment except in the case of the anacephalic monster which probably was unrelated to the therapy.

Methylthiouracil was given to six mothers. The case reported by Elphinstone (22) had mental retardation

TABLE VII

FETAL ABNORMALITIES ATTRIBUTED TO THE ANTITHYROID DRUGS

Medication	Abnormality	Results	Source
Thiouracil .6 gm./day for 4 mon., .4 gm./day for 1 mon., .2 gm./day for 3 mon.	Enlarged thyroid	Decreased in size. Baby lived.	Eaton (20) 1945
Thiouracil .6 gm./day for 4 wks., .4 gm./day for 4 wks.	Increased blood organic iodine and low cholesterol	Baby lived.	Strouse & Drabkin (51) 1946
Thiouracil .4 gm./day for 13 wks.	Anacephalic Monster with cleft palate		Whitelaw (55) 1947
Thiouracil for 9 mon.	Enlarged thyroid	Normal by 1 mon.	Verel (53) 1949
Thiouracil	Goiter & vomiting		Keynes (35) 1952
Thiouracil	Goiter		Keynes (35) 1952
Thiouracil	Cretin		Keynes (35) 1952
Thiouracil	Cretin		Keynes (35) 1952
Thiouracil	Cretin		Keynes (35) 1952
Methylthiouracil .2-.3 gm./day through preg.	In 2nd mon. developed exophthalmos, low cholesterol & mental changes.	Normal by 5th mon.	Frisk (28) 1947
Methylthiouracil .6 gm./day for 3 wks, .1 gm./day for 5 wks., Nothing for 4 mon., .1 gm./day for 1 mon.	Cretin	Baby lived	Ball & Morrison (8) 1948
Methylthiouracil .2 gm./day for 4 mon., .1 gm./day for 3 mon.	Cretin	Died soon after birth.	Hone & Magarey (31) 1948

TABLE VII CONTINUED

FETAL ABNORMALITIES ATTRIBUTED TO THE ANTITHYROID DRUGS

Medication	Abnormality	Results	Source
Methylthiouracil .2 gm./day for last 4½ mon.	Enlarged thyroid & hypothyroidism	mental retardation & hypothyroid at 17th mon.	Elphinstone (22) 1953
Methylthiouracil .2 gm./day for last 5 mon.	Hypothyroid	Baby lived	Morris (40) 1953
Methylthiouracil .1 gm./day for 9 mon.	Enlarged thyroid with dystocia	Normal by 1 mon.	Marussi-Scarizza (39) 1954
Propylthiouracil .1-.2 gm./day for last 6½ mon. Lugol's 10 gtts. t.i.d. added last mon.	Enlarged thyroid. 2 mon. premature.	Baby died (Authors feel drugs not cause)	Seligman & Pescovitz (47) 1950
Propylthiouracil .15-.20 gm./day for last 2 mon.	Enlarged thyroid. Born prematurely.	Baby lived	Seligman (48) 1950
Propylthiouracil .25 gm./day throughout pregnancy.	Enlarged thyroid.	Soon normal	Hepner (30) 1952
Propylthiouracil .1 gm./day plus 10 gtts. of Lugol's solution t.i.d. for last 5 mon.	Enlarged thyroids (twins)	One stillborn, other lived	Saye, et al., (46) 1952
Propylthiouracil .3 gm./day for all of pregnancy	Goiter	Soon normal	Aaron (1)1955

at seventeen months of age. This points out the important fact as discussed previously in another chapter that an overdose of an antithyroid drug given to the mother will produce myxedema and subsequent hypothyroidism in the baby. This case, therefore, cannot be used as an indication against the drug but rather for moderation and adequate clinical and laboratory evaluation. One baby died soon after birth following the administration of 0.1-0.2 gm./day to the mother from the second month of pregnancy to term. The rest of the mothers in whom the dose was known were subjected to a dose of 0.2-0.3 gm./day. These babies all lived and were normal in a few weeks after delivery. There was no permanent impairment observed in any of the infants except in the case of mental retardation.

Five mothers received propylthiouracil. One mother gave birth to twins. Both babies had an enlarged thyroid and one was stillborn. The mother had received 0.1 gm. of propylthiouracil per day plus ten drops of Lugol's solution three times a day for the final five months of her pregnancy. Seligman (47) reports a death in a baby born two months prematurely. He feels that drugs were not the major factor in the cause of death. The mother of another baby that was born prematurely had been treated with 0.15-0.2 gm. of propylthiouracil per day

for the last month. The rest of the babies experienced a gradual decrease in the size of the thyroid to normal within a short time. Two patients received Lugol's solution in addition to propylthiouracil. The dose of propylthiouracil used by these authors ranged from 0.1-0.3 gm./day. Of the babies that lived there was no permanent impairment noted.

In 1945 Eaton (20) treated two patients with thiouracil. He stopped the thiouracil four weeks before delivery in one and gave Lugol's solution. The patient gave birth to a normal infant. The other patient received no iodine and the offspring had a goiter. He recommends that iodine be given to prevent enlargement of the fetal gland. The cause, in his opinion, is probably thyrotropin or thiouracil in the fetal circulation. Three years later Hone and Magarey (31) recommended that the antithyroid drug be stopped three weeks prior to delivery and iodine started. Verel (53) in 1949 also treated one patient with thiouracil and stopped the drug two months prior to the expected date of confinement and gave the mother ten minims of Lugol's solution daily. The baby was normal.

In table VII two patients were treated with iodine in addition to propylthiouracil (Seligman (49) and Saye, et al. (46). One mother received 0.1-0.2 gm.

of propylthiouracil daily for the last six and one-half months of pregnancy and ten drops of Lugol's solution three times a day was added for the final month of her pregnancy. The other patient received 0.1 gm. of propylthiouracil per day plus ten drops of Lugol's solution three times a day for the last five months prior to term. Both of these babies had goiter. Heinemann, Johnson and Man (63) in 1948 and Hepner (30) in 1952 gave both iodine and thiourea derivatives for the last month of gestation and reported no infantile goiters.

Bain (7) followed one case case in 1947 which he treated with ten drops of Lugol's three times a day plus 0.45 gm. of propylthiouracil per day for the last two months prior to delivery. The infant was normal. Two normal babies were delivered in 1948 by Reveno(43) after one mother had received 0.1 gm. of propylthiouracil per day for four months with the addition of fifteen minums of Lugol's solution daily for the last three weeks before the end of her gestation. The other patient received 0.15 gm. of propylthiouracil daily for the last eight months of her pregnancy with the addition of fifteen minims of Lugol's solution daily for the final three weeks. One other case was reported by Eisenberg (21) in 1950 in which the mother had received 0.3 gm. of propylthiouracil for the last month of her

pregnancy plus ten drops of Lugol's solution three times a day for the three week period prior to the delivery of a normal infant.

Williams (58) states that the safest regime is two-thirds the usual dose of tapazole or propylthiouracil plus five drops of KI daily. Fifteen infants in his study were all normal with no prematures. To show his point he quotes Astwood who used antithyroid drugs without iodine and had three pre mature births with no deaths in twenty-two babies. McGavack (145) also suggests the use of small doses of iodine with these compounds.

Spontaneous abortion may result from hypothyroidism in the mother introduced by the antithyroid drugs (55, 62). This is more apt to cause fetal loss if it occurs early in the pregnancy whereas myxedema later in the pregnancy is not inconsistent with a normal outcome, although, the fetal thyroid may be enlarged (4).

Two babies that were born prematurely are reported in Table V by Seligman (47, 48). One of these babies died. Abrupto placenta was reported by Palmer (41) in a patient being treated with thiouracil.

Caren (15) and Keynes (35) writing in 1949 and 1952 respectively, feel that even though the infant is normal at birth it does not necessarily mean that the

thyroid is functioning normally as the goitrogen may depress the fetal thyroid and still go unnoticed. Due to this uncertainty they distrust its use. Other authors feel that goiter in the infant may be attributed to prolonged use (26) or to over dosage (35, 40).

There is general agreement that the antithyroid drugs cross the placental barrier (27, 58). The question than arises as to whether the fetal gland is enlarged because of the thyrotropin or the thiouracil (20). Assuming that thiouracil can reach the fetal circulation, we could then postulate that it would be able to inhibit the synthesis of thyroxine by the fetal gland (28). This, of course, would imply a functioning fetal thyroid. We could further reason that with a decreased thyroxine level in the fetal circulation, as none is diffusing across from the mother and the fetus is making none, that there would be an increase in thyrotropin. This could then cause an enlarged and hyperplastic thyroid (10, 15, 18, 19, 20, 27, 29, 35, 42). If thyrotropin is able to gain access to the fetal circulation, then this too would be able to cause an enlarged fetal thyroid.

If both substances are transmitted across the placental membranes the fetus is hardly effected by the antithyroid substances as such but rather on the amount of thyroxine present (27). Theoretically, if the BMR

is normal for the pregnat state, there is no danger of hurting the baby (27, 145) or causing hypertrophy of the maternal thyroid (4). If the mother is myxedematous the baby would suffer the same fate (27, 28). Supposing that the BMR is euthyroid for pregnancy the thyroxine would prevent myxedema in the fetus and decrease the excessive fetal thyrotropin activity and prevent an enlargement of the baby's thyroid (4, 6, 27).

There is agreement in the literature that the hyperthyroid mother should not nurse her infant. The reasons are: a. the presence of toxic products in the milk (14, 128), b. the additional strain on the mother (128) and c. the transmission of the antithyroid substances in the milk (14, 27, 32, 62, 98, 145, 175, 186, 189). This has been easily demonstrated by giving two mothers 1.0 gm. of thiouracil. Two hours later the serum concentration was 4 mgm. % and 3.2 mgm. % with a milk concentration of 12 mgm. % and 9.2 mgm. % respectively.

In table VIII are tabulated ninely-six normal infants reported in the literature as being delivered from mothers receiving antithyroid therapy. The highest amount of thiouracil given during a pregnancy is reported by King and Collen (36) as 0.6 gm./day for one month followed by 0.1-0.2 gm./day for four months and then

TABLE VIII

NORMAL BABIES DELIVERED FROM MOTHERS RECEIVING ANTI-THYROID THERAPY

No. of Cases	Medication	Source
1	Thiouracil	Astwood (5) 1944
1	Thiouracil	Davis (74) 1944
1	Thiouracil	McGavack, et al. (38) 1944
1	Thiouracil	Rose & McConnell (172) 1944
1	Thiouracil	Palmer (41) 1945
3	Propylthiouracil	Astwood & Vanderlann (6) 1946
1	Thiouracil .6 gm./day for 1 mon., 4 gm./day for 3 mon. Stopped for 1 mon. NaI 2 minims/day for 18 days. Thiouracil .6 gm./day for 13 days, 1.2 gm./day for 1 wk.	Carns & Poser (16) 1946
1	Thiouracil derivatives	Josefson (34) 1946
2	Thiouracil (1 patient maintained on .15 gm./day.)	Sexton (49) 1946
1	Methylthiouracil for 4 mon.	Vogt (54) 1946
5	Thiouracil given to 3 patients for entire pregnancy, one for last 6 wks. and one for last 4 wks.	Williams (57) 1946
1	Thiouracil .6 gm./day for 2 mon. .1 gm. per day for 1 mon., .6 gm./day for 1 mon.	King & Collen (36) 1947
1	Thiouracil .6 gm./day for 1 mon., .1-.2 gm./day for 4 mon., .4-.6 gm./day for last 3 mon.	King & Collen (36) 1947
1	Thiouracil	Whitelaw (55) 1947
9	Thiouracil for 1 mon.or longer.	Williams, et al. (56) 1947
3	Thiouracil throughout pregnancy. (1 patient given .2 gm./day for last 3 mon.)	Williams, et al. (56) 1947

TABLE VIII

NORMAL BABIES DELIVERED FROM MOTHERS RECEIVING ANTI-THYROID THERAPY

No. of Cases	Medication	Source
1	Thiouracil in early pregnancy only.	Mussey, et al. (98) 1948
1	Thiouracil for first 2 mon then propylthiouracil to term.	Reveno (43) 1948
1	Thiouracil .1 gm./day for first 2 1/5 mon. of pregnancy.	Acton & Cottrell (3) 1949
1	Thiouracil .6 gm./day for 5 wks, propylthiouracil .15 gm./day for last 4 3/4 mon. of pregnancy.	Caren (15) 1949
5		McGavack (145) 1949
1	Propylthiouracil .15 gm./day for 2 mon., .075 gm./day for 5 mon.	Ryan & Kooperstein (44) 1949
1	Thiouracil - stopped 4 days before E.D.C.	Verel (53) 1949
1	Propylthiouracil .075 gm./day for 2 wks., .15 gm./day for 2 wks., .25 gm. per day for 2 wks., .15 gm./day for 3 wks., .2 gm./day for 2 mon.	Saslow & Kroff (45) 1950
13	Propylthiouracil .3 gm./day until euthyroid then .15 gm./day.	Astwood (4) 1951.
1	Mercaptoimidazole 1.0 gm./day decreasing with clinical responce.	Astwood (4) 1951
2	Methylmercaptoimidazole .015 gm./day	Astwood (4) 1951
3	Propylthiouracil started and later changed to methylmercaptoimidazole.	Astwood (4) 1951
4	Thiouracil	Trotter (52) 1951
3	Propylthiouracil .15-.2 gm./day decreasing to 0.05 gm./day for 1st trimester only.	Seligman (48) 1952
2	Propylthiouracil .15-.2 gm./day decreasing to .05 gm./day for last mo.	Seligman (48) 1952
1	Thiouracil .6 gm./day from 3-5th mo.	Sirven & Navarret (50) 1952
10		Piper & Rosen (42) 1954
12	Thiouracil for a short time.	Keynes (35) 1955

0.4-0.6 gm./day for three months. Carns and Poser (16) employed the highest daily dose which was 1.2 grams.

The greatest amount of propylthiouracil used during a gestation was 0.075 gm. daily for two weeks, 0.15 gm./day for two weeks, then 0.25 gm. daily for two weeks followed by 0.15 gm./day for three weeks and concluded with 0.2 gm. daily for two months (45). The highest individual dose of propylthiouracil was 0.3 gm./day used by Astwood (4).

CHAPTER VI

IODINE IN THE MANAGEMENT OF THE PREGNANT AND HYPERTHYROID PATIENT

Strause and Daly (134) in 1925 reasoned that pregnancy, by increasing the need for thyroid activity, could cause an excessive demand on the thyroid gland, resulting in a diminished iodine content. Thus, if the iodine intake was inadequate there could be a physiological overstrain of the gland giving a clinical picture of hyperthyroidism. In their series they saw sixty-one such patients who responded to iodine therapy. Their study slong with McGavack's (145) suggests that iodine given under cautious control could prevent this syndrome. McGavack (145) advocates the prophylatic use of iodine in all women living in an endemic goiter zone or in whose family it is a common occurence.

Charpentier (2) in his Cyclopoedia of Obstetrics and Gynecology written in 1887 states, "Goiter in pregnancy is usually benigh and should be treated by general measures and internal treatment. Forbid the patient to nurse and give iodine." This was followed for some time by an attempt to control hyperthyroidism in pregnancy with rest sedatives and Lugol's solution, ten drops, three times a day (13, 18, 24, 60,

73, 74, 79, 85, 86, 97, 98, 100, 101, 103, 104, 109, 112, 113, 116, 156, 161, 169, 234, 237, 238), with a hope of carrying the patient to term. It was observed as pointed out before that many times the symptoms of the patients would disappear with delivery (24, 238). It has been reported that in some cases iodine fails to stop the course of the disease and in these patients thyroidectomy is recommended after two weeks of trial therapy (13, 60, 67, 84, 85, 97, 100, 103, 112, 116, 156, 168, 234, 237). As is well known hyperthyroid patients may become resistant to prolonged iodine therapy causing a loss of its usefullness. In the interum perhaps all that has been gained is a false sense of security (83, 96, 101, 103, 156). There have, however, been reports in the literature in which iodine was given over long periods of time without development of a thyroid crisis (24, 25, 236). This has led Falls (24, 25, 236) to postulate a difference in the pregnant patients.

Hinton (75) and Graham (235) treat both adenomous and diffuse goiter with iodine. There seems to be some disagreement on this point. The use of iodine in Graves' disease is not contested (25, 67, 83, 96, 97, 98, 103, 112, 113, 156). However, some authors feel iodine should not be used in adenomatous goiter (112)

for fear of making one toxic or more toxic (60, 79, 83, 96, 113, 160), or having little or no influence on this disease (96, 97, 103). Falls (24, 25) and Hyman (149) on the other hand have no objections to its use although Brandes (67) states nodular goiter is less amenable to this form of therapy. Jackson (86) restricts the use of iodine in adenomatous goiters to mild cases.

There are ninety-seven cases of iodine treated hyperthyroidism complicating pregnancy reported in the literature. These are summarized in Table IX. In this series of patients, eighty-four or 86.5% of the babies were carried to term. There were nine prematures (74, 121, 129), one spontaneous abortion (87), three fetal deaths (20, 79, 121) and two maternal deaths after delivery (60, 97). Twelve patients (12.4%) had nodular goiter, the rest were diffuse in type.

TABLE IX

PREGNANCY COMPLICATED BY HYPERTHYROIDISM WHICH WAS TREATED WITH IODINE ALONE

No. of Cases	Type	No. to term	Source
7	Diffuse	3	Kosmok (121)
3	Nodular	3	Mussey & Plummer (95)
4	Nodular	4	Falls (79)
13	Moderate Hyper-thyroidism	13	Falls (79)
5	Diffuse	5	Falls (79)
2	Diffuse	2	Reycraft (104)
1	Nodular	1	Mussey & Plummer (96)
7	Diffuse	7	Mussey & Plummer (96)
5	Mild hyper-thyroidism	5	Bothe (60)
3	Diffuse	3	Mussey (97)
18	Diffuse	13	Javert (87)
3	Diffuse	3	Baumgartner (9)
4	Nodular	3	McLaughlin & McGoogan (129)
7	Diffuse	6	McLaughlin & McGoogan (129)
7	Diffuse	6	Davis (74)
2	Diffuse	1	Eaton (20)
3	Diffuse	3	Mussey, et al. (98)
3	Diffuse	3	Acton & Cottrell (3)
97		84	TOTAL

CHAPTER VII

THE TREATMENT OF HYPERTHYROIDISM COMPLICATING PREGNANCY WITH THYROIDECTOMY

There are numerous reports in the literature in which the feeling is strong for treating hyperthyroidism complicating pregnancy with thyroidectomy after adequate preparation with iodine (13, 17, 35, 69, 75, 78, 81, 84, 85, 86, 91, 94, 104, 133, 169). Other authors favor this method of treatment only if the thyrotoxicosis is severe (18, 60, 61, 65, 71, 97, 98, 101, 103, 145). Some workers favor the operation of all cases of nodular goiter in pregnancy (26, 61, 67, 82, 98, 102, 133) unless it is in the last six weeks of gestation and even then if the BMR is greater than plus 50% or if signs of mycardial insufficiency or dyspnea are present (24, 97, 103, 156, 168). The reasons for operating all of these are given as the impending organ damage secondary to the prolonged course of the disease (102) and the danger of carcinoma (82, 133).

Crile (17) in 1950, Keynes (35) and Bartels (180) in 1952 and Marussi-Scarizza (39) in 1954 reported the use of thiouracil derivatives as an aid in the preparation of severely toxic patients. But even then they used small doses for a short period of time with the exception of

Bartels (180) who uses the drugs until the patient is euthyroid. He feels this decreases the operative mortality.

There is considerable discussion as to when the thyroidectomy should be performed if it is going to be done during the gestation. It is generally agreed that the best time is early, usually before the third or fourth month (18, 26, 50, 65, 66, 70, 74, 76, 96), as there seems to be a definite mortality factor if it is performed at a later date (91). Other authors divide the line at five to six months (39, 50, 59, 78, 180) and treat all patients medically after that time. Dailey and Benson (84) noted an increased incidence of postoperative abortion when the surgery was done during the first trimester. Greenhill (62) feels there is n o increased hazard after the third month.

In the management of this type of surgery Falls (99) likes to give his patients corpus luterum ex tract to decrease the irritability of the uterus during the proceedure. It should also be recalled that the thyroid is hyperplastic with the pregnant state and will automatically recede to a certain degree after delivery. In consequence too radical a procedure may cause a severe post partum hypothyroid condition (18).

As there are those who favor thyroidectomy

during pregnancy there are those who argue against it (14, 77, 83, 87, 88, 93, 109), do to the increased risk (111), increased maternal mortality (79) and the increased fetal loss (24, 35, 50, 58, 68, 98, 99). The latter has been reported as ranging from 6-33% by Sirven and Navarret (50). These authors would perform a thyroidectomy after delivery if indicated at that time. Wallace (112) feels there is no increased risk or mortality with thyroidectomy. It is interesting to note that Jackson (86) finds that the younger the patient, the greater is the degree of hyperthyroidism and the greater the risk in exopthalmic goiter. The risk was found to be less if the patient was operated early in the course of Graves' disease.

It is generally agreed that if the patient has a thyroidectomy she should not become pregnant for 18-24 months (26, 81, 89, 112, 115). As will be pointed out in a later chapter this may be an indication for a therapeutic abortion should the patient become pregnant. Nevertheless, Wallace (112) has observed patients who became pregnant sooner and who had no adverse effects.

In Table X I have summarized five hundred and fifty-seven cases of hyperthyroidism complicating pregnancy which were treated by thyroidectomy. Of this series there were 60 (10.8%) fetal deaths and five (0.9%) maternal

TABLE X

SURGICAL MANAGEMENT OF HYPERTHYROIDISM COMPLICATING PREGNANCY

No. of Cases	Complications	Source
7	One maternal death	Schmauch (105) 1913 Quoted from # 86.
7	None	Seitz (106) 1913
5	None	Beck (65) 1921
6	None	Boys (66) 1923
1	None	Davis (73) 1926
22	Three stillbirths	Mussey, et al. (95) 1926
1	None	Yoakum (116) 1928
8	One spontaneous abortion	Falls (79) 1929
1	None	Davidson (72) 1929
2	One spontaneous abortion	Falls (79) 1929
15	One spontaneous abortion	Clute and Daniels (69) 1930
1	One stillbirth	Fahrni (78) 1930
1	None	Reycraft (104) 1930
15	One spontaneous abortion	Lahey (91) 1931
7	None	Frazier and Ulrich (85) 1932
1	None	Polome (100) 1932
5	None	Bothe (13) 1933
28	One fetal death	Lehman (92) 1933
5	None	Bothe (60) 1935
2	None	Portis and Roth (101) 1939
66	Two premature deaths, two stillbirths and two spontaneous abortions	Mussey (97) 1939
1	Premature monster	Wallace (113) 1940
6	One spontaneous abortion	Baumgartner (9) 1942
8	One stillbirth, one maternal death	McLaughlin and McGoogan (129) 1943
3	One spontaneous abortion	Kibel (90) 1944
1	None	Stepto (110) 1946
94	Six spontaneous abortions and two maternal deaths.	Brandes (67) 1948

TABLE X CONTINUED

SURGICAL MANAGEMENT OF HYPERTHYROIDISM COMPLICATING PREGNANCY

No. of Cases	Complications	Source
30	None	Mussey (98) 1948
33	One maternal death	Crile (17) 1950
21	One spontaneous abortion, two prematures (1 died), one stillbirth, one died after Cesarean section	Bell (59) 1950
27	One spontaneous abortion, two premature deaths, two stillbirths and one died after Cesarean section	Bartels (180) 1952
21	One stillbirth and two spontaneous abortions	Dailey and Benson (84) 1952
21	One stillbirth	Keynes (35) 1952
3	One premature	Sirven and Navarret (50) 1953
42	Fifteen fetal deaths	Williams (58) 1955
257		TOTAL

deaths following surgery. The breakdown of the fetal deaths was nineteen spontaneous abortions, fourteen stillbirths, eight premature deaths and nineteen unclassified fetal deaths.

CHAPTER VIII

THE ROLE OF THERAPEUTIC ABORTION IN THE MANAGEMENT OF HYPERTHYROIDISM COMPLICATING PREGNANCY

The preponderence of opinion is that a patient who has hyperthyroidism and is pregnant should not be aborted (26, 42, 68, 74, 84, 86, 92, 94, 95, 97, 101, 103, 109, 111, 116, 122, 145, 156, 169). These authors feel that a therapeutic termination of the pregnancy may be followed by a thyroid crisis and death. If the disease is mild there would be no indication for such a proceedure. Some authors favor therapeutic abortion (77, 240) if the disease is severe (15, 149), if mild (60), if early in the pregnancy (75, 78, 83), if the patient had toxic nodular goiter for a long period of time (128), or if the patient gets pregnant within eighteen months after a subtotal thyroidectomy (81).

Dannreuther (244) in 1946 reported eighty-four cases of therapeutic abortion done in a general hospital. Of this number nine had hyperthyroidism. Three were severe, five had persistence of symptoms after thyroidectomy and one had recurrence of carcinoma of the thyroid. In Table XI I have summarized fifteen cases of therapeutic abortion performed on two hundred and ten patients with hyperthyroidism reported in the literature. The incidence is 7.1% in this series. Barm (128) reported a 10% incidence in 1936.

TABLE XI

INCIDENCE OF THERAPEUTIC ABORTIONS IN HYPERTHYROIDISM COMPLICATING PREGNANCY

No. in series	No. with therapeutic abortions	Source
112	5	Seitz (106) 1913
33	1	Lehman (92) 1933
14	1	Portis and Roth (101) 1939
18	4	Javert (87) 1940
12	1	Kibel (90) 1944
21	3	Dailey and Benson (14) 1952
210	15	TOTAL

CHAPTER IX

RADIOACTIVE IODINE AND X-RAY THERAPY

The fetal thyroid has been said to be functioning actively in early embryonic life (17, 35, 256), by the end of the sixth month (55, 255), at birth (258) and not until sometime after birth (119, 123). We might reason that if radioactive iodine is given to a pregant patient and if the fetal thyroid is functioning, it will be destroyed and possibly cause ill effects on the fetus (18, 35, 256). However, it has been given inadvertently with no ill effects (58). Recent work by Chapman, et al. (254) indicates that the human fetal thyroid does not collect radio iodine in the first twelve weeks of life and that increasing amounts are collected after the fourteenth week. They conclude that pregnant women may be given therapeutic doses of radioiodine without retention of this radioactivity by the fetus if given prior to the fourth month of gestation. These authors have treated one woman in the second month and one in the sixth month with no untoward effects on the child. Means (169) writing in 1948 agrees with this work.

X-ray therapy has been used safely to control the symptoms of hyperthyroidism in pregnancy (18, 57, 74

84, 86) but the final effect may not be achieved for seven to eight months (84). As with surgery, it is hard to tell how much tissue to remove from active functioning and thus is a possable indication against its use as hypothyroidism may result. Williams (57) treated 7% of his patients with thiouracil and iodine in addition to irradiation. He used five treatments at weekly intervals with two hundred and ten r to each lobe. Even though some required a second course, he was successful in controlling the symptoms of hyperthyroidism in pregnancy.

CHAPTER X

ADJUNCTIVE THERAPY

Specific methods of therapy for hyperthyroidism complicating pregnancy have been given. The following adjunctive therapeutics have also been advocated: a. high caloric diet (11, 50, 89, 145); b. vitamins (11, 41, 50, 89, 145, 156); c. rest (50, 145); d. sedation (41, 50, 145); e. psychotherapy (145); f. vitamin D and possably calcium (89, 145); g. cevitanic acid to counteract marrow depression in antithyroid drug therapy (41) and h. liver extract.

CHAPTER XI

REPORT OF CASES

In a previous report McLaughlin and McGoogan (129) reported the cases of hyperthyroidism complicating pregnancy from 1932-1942 at the University of Nebraska Hospital in Omaha. In the period from 1943-55 there were 6,790 deliveries including stillbirths at this hospital. There were three patients who had a complicationg of hyperthyroidism giving an incidence of 0.04%. A presentation of these cases follows:

Hospital number 108029: This 22 year old para 1, gravida 2, entered UNH at approximately six months of gestation. Seven months prior this white woman first noted symptoms of headache, nervousness, swelling in her neck, tremor, weight loss and increased sweating. Physical examination at this time revealed stare, exopthalmos, convergence weakness, lid lag, widened palpebral fissures, a blood pressure of 130/80 and a pulse range of 74-100. Her BMR was plus 49% and she had a diffusely enlarged and firm thyroid gland measuring 4 x 10 cm. Approximately five months ago the symptoms had progressed to the point that she was given 10 mgm. of tapazole three times a day,

30 mgm. of phenobarbital four times a day, rest and a high protein-high carbohydrate died. The symptoms gradually decreased until the present admission but she was still considered mildly toxic. The tapazole was discontinued shortly after her admission. She was delivered by her family physician. The results are unknown.

Hospital number 121,037: This 20 year old para 2, gravida 3, entered UNH for the first time at approximately three months of gestation. This white woman first noted heat intolerance, nervousness, fatigue and increased appetite for three months and a choking sensation for two months. On admission her thyroid was diffusely enlarged to two times its normal size. Her blood pressure ranged from 146/62 to 120/60 and her pulse from 60-120. She had quadriceps weakness, hyperactive reflexes, lid lag, loss of convergence and infrequent winking but no exopthalmos. Her radioiodine uptake was 65.5% in 20 hrs. and her BMR was 22%. She had a WBC of 10,700 with a normal differential. The impression was mild thyrotoxicosis, intrauterine pregnancy and psychoneurosis, phobic reaction. She was treated with 30 mgm. of phenobarbital four times a day.

She was seen again at eight months of gestation

with no change or slight improvement of her symptoms. She was delivered by her family physician. The results are unknown.

Hospital number 122,460: This para 3, gravida 4, colored woman entered UNH for the third time at approximately thirty-eight weeks of gestation. Ten months prior she had been diagnosed as hyperthyroid. Her symptoms were a mass in her neck, dyspnea, sweating, nervousness, tremor, and excessive appetite. At that time she had a BMR of 74% and 76% and an iodine pickup of 73% in 24 hrs. She was treated with 6,000 m.c. of radioiodine and one week later she started to take 5 mgm. of tapazole three times a day. Her symptoms improved until toxic symptoms developed eight months prior to admission. At this time her iodine pickup was 77% in 24 hrs. Therefore, she was given 3,000 m.c. of radioiodine. The tapazole was stopped in one week.

Six months prior to admission her radioiodine pickup was considered to be normal but her pulse rate was 100-130. The size of the uterus was compatable with a three to four months gestation. Approximately six weeks prior to admission her iodine pickup was 83% in 24 hours. She had slight exopthalmos and a pulse rate of 120. She was started on two drops of Lugol's solution three times

a day.

On the present admission her thyroid had slight diffuse enlargement and she had slight exopthalmos. Her pulse rate varied from 70-100. Her blood pressure was 112/70. The impression was mild thyrotoxicosis with pregnancy. She had an uneventful deliv ry two weeks later. She was seen three months later and her iodine uptake was 99% in 24 hours and her BMR was plus 39% and plus 34%. She was given an additional 4,000 m.c. of radioiodine. At the present time this patient is approximately six months along with another pregnancy and so far has had no signs of hyperthyroidism.

CHAPTER XII

SUMMARY AND CONCLUSION

The incidence of hyperthyroidism in pregnancy varies from 3.7% to 0.03% with an average of 0.057%. Pregnancy in hyperthyroidism occurs in 3.2%-0.2% of the cases reported in the literature with an average incidence of 0.74%. The relative rarity has been attributed to the sterility induced by the disease and a peak incidence of hyperthyroidism at a time late in the reproductive era.

Hypertrophy of the thyroid gland occurs in approximately 31% to 90% of all pregnancies. Hypertrophy is more frequent in older patients, in women with large families and in those patients who have given birth to several children in rapid succession. Associated with the hyperactivity of the thyroid gland there is an increase in the blood iodine, BMR, SPI, secretion of adrenalin and ketone bodies in the blood and urine. Simultaneously there is a decrease in the serum cholesterol, iodine content of the thyroid gland, liver glycogen and insulin effect. A redistribution of calcium is also noted. The normal variations seen in the pregnant state of these values has been discussed. Clinical evaluation plus these laboratory determinations offer valuable aid in studying the progress and severity of the disease and

grant insight into the adequacy of the therapy.

The acute type of hyperthyroidism, Graves' disease is characterized by an abrupt onset of toxic symptoms, periods of remission and a higher BMR than nodular goiter. As this disease has a peak incidence at a younger age then adenomatous goiter it occurs approximately three times more frequently.

Nodular goiter, the chronic form of hyperthyroidism is characterized by a gradual onset of toxicity. The disease is progressive and tends to produce serious damage to vital organs which may predispose to complications with the onset of labor.

The majority of the cases of hyperthyroidism are probably made worse by pregnancy but nevertheless a good percentage are not affected or are even aided by the gravid state. Hyperthyroidism causes an elevation of the fetal mortality and is believed by some to play a role in the etiology of toxemia of pregnancy.

With the onset of labor, the patient should not be allowed to strain, pain should be avoided, the second stage of labor should be shortened and postpartum hemorrage should be anticipated. The babies born to untreated mothers are normal and healthy. Following the termination of the pregnancy, these women should be observed frequently for thyroid evaluation. They probably

should not get pregnant for several months to a year.

Propylthiouracil and tapazole have proven to be the drugs of choice in the management of these patients. They have the lowest incidence of toxic reactions of any of the thiouracil derivatives. These drugs have proven to be uniformly effective in maintaining a euthyroid pregnant state--which is the goal of therapy. If this atate is maintained, theoretically, there would be no danger to the baby and no maternal hypertrophy. A dose of two-thirds to three-fourths the regular amount will usually be enough. Occasionally some people will respond better if they are switched to the other drug. It is probably best to use small doses of iodine with these preparations. The patients should be carefully observed for fever, sore throat, skin reactions, leukopenia or granulocytopenia.

A series of one hundred and thirty pregnancies reported in the literature as having received thiouracil derivatives are presented. There were two maternal deaths (1.54%) and three (1.95%) had adverse side reactions. A group of one hundred and seventeen infants delivered from mothers receiving these derivatives are also presented. Ill effects consisting primarily of thyroid enlargement and cretinism were noted in twenty-one babies. There were two deaths (1.7%). There was no correlation in either the maternal group of the infant group between

dose given and adverse reaction encountered.

There is some indication that iodine alone or in combination with one of the other antithyroid drugs may permit the physician to carry his patient to term. The fact that the patient may become iodine fast should always be considered. Iodine has a disputed role in the treatment of adenomatous goiter. Ninety-seven cases of patients receiving iodine alone are presented. Eighty four of these or 86.5% went to term. There were nine prematures, one spontaneous abortion, three fetal deaths and two maternal deaths. The antithyroid drugs may grant the patient a cure, on the other hand if one can merely carry the patient to term, surgery could be evaluated at that time. In any event these patients should not nurse their offspring.

Thyroidectomy after preparation with iodine or in the more serious cases with one of the other antithyroid derivatives can be preformed anytime but preferably before the third trimester. The surgeon must be able to remove exactly the right amount of tissue. If he fails, hypothyroidism may result now, causing spontaneous abortion or myxedema or may result later leading to postpartum myxedema. Corpus luteum extract has been advocated to decrease uterine irritability during the thyroid surgery.

I have presented five hundred and fifty-seven cases of hyperthyroidism complicating pregnancy which were treated by thyroidectomy. There were sixty fetal deaths (10.8%) and five maternal deaths (0.9%). After this surgical proceedure and termination of the pregnancy at term, the patient should not get pregnant for eighteen to twenty-four months. If she does, this may be an indication for therapeutic abortion. There is no other indication for therapeutic abortion in hyperthyroidism complicating pregnancy.

The fetal thyroid does not pick up radio-iodine for the first twelve to sixteen weeks of gestation. Theoretically, if it is given during this time there will be no adverse effects. There are reports given in the literature as well as one of the case reports in this paper in which it was given at a later date and no abnormal effects were noted. This method of treatment as well as X-ray may take several months for the desired results to be reached and even then it is hard to gauge the accurate dose.

In addition to the specific methods of treatment already mentioned, the patient should also receive a high caloric diet, vitamins, rest, sedation, vitamin D and possibly liver extract.

Three case histories from University Hospital

are presented. All of these patients were in their early twenties and had Graves' disease. One was treated with phenobarbital, one with tapazole and one with tapazole and radio-iodine.

CONCLUSIONS:

1. The simultaneous existence of pregnancy and hyperthyroidism is rare.

2. Hypertrophy of the thyroid gland in pregnancy is common.

3. The thyroid gland is in a state of hyperactivity with pregnancy. Quantitative laboratory examination and clinical evaluation grant the physician a method of evaluating the normal and pathological phases of this increased activity.

4. Propylthiouracil or tapazole with iodine in doses to maintain the pregnant euthyroid state are effective and safe.

5. If the symptoms are not adequately controlled or progressing at an alarming rate, thyroidectomy during the first trimester is the treatment of choice.

6. When the patient goes into labor, she should not be allowed to strain, pain should be avoided , the second stage should be shortened and postpartum hemorrhage should be anticipated.

8. Therapeutic abortion is not indicated.

9. Statistical summary of maternal and fetal deaths by mode of treatment: (Table XII)

Treatment	No. in series	Maternal Deaths	Fetal Deaths
Thiouracil Derivatives	130	2 (1.5%)	
Thiouracil Derivatives	117		2 (1.7%)
Iodine alone	97	2 (2.0%)	4 (4.1%)
Thyroidectomy	557	5 (0.9%)	60 (10.8%)
TOTAL	901	9 (0.99%)	66 (7.3%)

10. The treatment of each case must be individualized to that particular person.

BIBLIOGRAPHY

1. Aaron, H. H., Schneierson, S. J., and Siegel, E.: Goiter in newborn infant due to mother's ingestion of propylthiouracil, J. A. M. A. 159: 848 1955.

2. Abbott, A. C., and Prendergast, J.: The histology of the thyroid gland in pregnancy, Canad. M. A. J. 34:609 1936.

3. Acton, W. C., and Cottrell, J. D.: Pregnancy in thyrotoxicosis under treatment with thiouracil, Canad. M. A. J. 61:27 1949.

4. Astwood, E. B.: The use of antithyroid drugs during pregnancy, J. Clin. Endocrinol. 11:1045 1951.

5. Astwood, E. B.: Thiouracil treatment in hyperthyroidism, J. Clin. Endocrinol. 4:229 1944.

6. Astwood, E. B., and Vanderlaan, W. P.: Treatment of hyperthyroidism with propylthiouracil, Ann. Int. Med. 25:813 1946.

7. Bain, L.: Propylthiouracil in pregnancy, South. M. J. 40:1020 1947.

8. Ball, K. P., and Morrison, B.: Thyrotoxicosis in mother with cretinism in child, Proc. Roy. Soc. Med. 41:195 1948.

9. Baumgartner, C. J.: Thyroid in pregnancy, California and West. Med. 57:307 1942.

10. Beck, A. D.: Obstetrical Practice, Baltimore, The Williams and Wilkins Co., 1951, p. 650.

11. Bissell, G. W.: Thiouracil: a review of its clinical indications, New York State J. Med. 45: 1643 1945.

12. Bodansky, M. and Duff, V. B.: The influence of Pregnancy on resistance to thyroxine with data on the creatine content of the maternal and fetal myocardium, Endocrinology 20:537 1936.

13. Bothe, F. A.; Hyperthyroidism associated with pregnancy, Am. J. Obst. & Gynec. 25:628 1933.

14. Bram, I.: Exophthalmic goiter and pregnancy, Am. J. Obst. & Gynec. 3:352 1922.

15. Caren, R. C.: The goitrogens in thyrotoxicosis complicating pregnancy, J. Clin. Endocrinol. 9:903 1949.

16. Carns, M. L., and Poser, R. F.: An evaluation of the present status of thiouracil therapy in thyrotoxicosis and a report of its use in twenty-two cases, Wisconsin M. J. 45:205 1946.

17. Crile, G., Jr.: Practical Aspects of Thyroid Diseases; Philadelphia and London, W. B. Saunders Co., 1950, pp.216-217.

18. Crotti, A.: A study based on forty-one years of thyroid surgery, J. Internat. Coll. Surgeons 13:697 1950.

19. Davis, L. J., and Forbes, W.: Thiouracil in pregnancy; effect on foetal thyroid, Lancet 2:740 1945.

20. Eaton, J. C.: Treatment of thyrotoxicosis with thiouracil, Lancet 1:171 1945.

21. Eisenberg, L.: Thyrotoxicosis complicating pregnancy, New York State J. Med. 50:1618 1950.

22. Elphinstone, N.: Thiouracil in pregnancy, Lancet 1:1282 1953.

23. Eugster, J.: Zur Erblichkeitsfrage der endemischen Struma, I-II, Arch, D. Julius Klaus-Stiftg. f. Vererbgsforsch 9:275 1934. Quoted from #145.

24. Falls, F. H.: Hyperthyroidism complicating pregnancy, Northwest. Med. 28:391 1929.

25. Falls, F. H.: The inter-relationship between the thyroid gland and pregnancy, Memphis M. J. 9:21 1932.

26. Ficarra, B. J.: Hyperthyroidism and pregnancy, Med. Times N. Y. 79:752 1951.

27. Freiesleben, E., and Kjerulf-Jensen, K.: Effect of 6-methyl-2-thiouracil on rat foetuses and infantile rats, Acta pharmacol. et toxicol. 2:307 1946.

28. Frisk, A. R., and Josefsson, E.: Thiouracil derivatives and pregnancy, Acta med. Scandinav. Suppl. 196:85 1947.

29. Goldsmith, E. D.: An analysis of the effects of continued thiourea treatment in pregnancy and on the development of the offspring in the rat, Am. J. Obst. & Gynec. 49:197 1945.

30. Hepner, W. R., Jr.: Thiourea derivatives and the fetus, Am. J. Obst. & Gynec. 63:869 1952.

31. Hone, G. M., and Magarey, I.: Cretinism associated with the methyl thiouracil therapy, Australian M. J. 2:524 1948.

32. Hughes, A. M.: Cretinism in rats induced by thiouracil, Endocrinology. 34:69 1944.

33. Jones, G. E. S.: The effect of thiouracil hypothyroidism on reproduction in the rat, Endocrinology, 38:337 1946.

34. Josefson, A.: Nord. med. 32:2710 1946. Quoted from #42.

35. Keynes, G.: Obstetrics and gynaecology in relation to thyrotoxicosis and myasthenia gravis, J. Obst. & Gynaec. Brit. Emp. 59:173 1952.

36. King, R. W., and Collen, M. F.: Thiouracil in the treatment of hyperthyroidism complicating pregnancy: presentation of two cases, Permanente Found. M. Bull. 5:15 1947.

37. Lund, J.: Ugesk. f. laeger. 112:671 1950. Quoted from #42.

38. McGavack, T. H., Gerl, A. J., Vogel, M., and Schwimmer, D.,: The treatment of twenty-six thyrotoxic patients with thiouracil and a review of toxic reactions in all (135) reported cases, J. Clin. Endocrinol. 4:249 1944.

39. Marussi-Scarizza, P.: Gozzo congenito in neonato da antitaroidei sommimstrati alla madre durante la gravidanza, Minerva Pediat. (Torino) 1954. Quoted from Excerpta Medica 8:428 1955.

40. Morris, D.: Transient hypothyroidism in a newborn infant, Lancet 1:1284 1953.

41. Palmer, M. V.: Hyperthyroidism and thiouracil, Ann. Int. Med. 22:335 1945.

42. Piper, J., and Rosen, J.: Management of hyperthyroidism during pregnancy, Acta med. Scandinav. 150:215 1954.

43. Reveno, W. S.: Propylthiouracil in the treatment of toxic goiter, J. Clin. Endocrinol. 8:866 1948.

44. Ryan, C. M., and Kooperstein S. I.: Propylthiouracil in treatment of hyperthyroidism complicating pregnancy, Bull. Margaret Hague Maternity Hosp. 2:32 1949.

45. Saslow, M. S., and Kroff H.: 6-n-propyl thiouracil in thyrotoxicosis complicating pregnancy, J. Florida M. A. 37:94 1950.

46. Saye, E. B., Watt, C. H., Foushee, J. C. and Palmer, J. I.: Congenital thyroid hyperplasia in twins, J. A. M. A. 149:1399 1952.

47. Seligman, B., and Pescovitz, H.: Suffocative goiter in new born infant, New York State J. Med. 50:1845 1950.

48. Seligman, B.: Short-term goitrogen therapy of toxic diffuse goiter complicating pregnancy, New York State J. Med. 52:1137 1952.

49. Sexton, D. L.: Thiouracil, South. Med. J. 39:891 1946.

50. Sirven, R. H., and Navarret, E. E.: Hyperthyroidism y embarazo, Rev. Asoc, Med. Argent. 66:254 1952. Quoted from Excerpta Medica 6:468 1953.

51. Strouse, S., and Drabkin, C.: Hyperthyroidism in pregnancy treated with thiouracil, J. A. M. A. 131:1494 1946.

52. Trotter, W. R.: 1951. Personal communication to author of #22.

53. Verel, D.; Thiouracil in thyrotoxicosis, Brit. M. J. 1:892 1949.

54. Vogt, E.: Erfaringer med methylthiouracil behandlung au threotoksikose, Nord. Med. 31:1773 1946. Quoted from #22.

55. Whitelaw, M. J.: The treatment of hyperthyroidism complicating pregnancy and its effect on the human fetal thyroid, J. Clinl Endocrinol. 7:767 1947.

56. Williams, R. H., Asper, S. P., Rogers, W. R., Myers, J. D. and Lloyd, C. W.: Persistence of remissions of thyrotoxicosis after cessation of thiouracil therapy, New England J. Med. 236:737 1947.

57. Williams, R. H.: Thiouracil treatment of thyrotoxicosis, J. Clin. Endocrinol. 6:1 1946.

58. Williams, R. H.: Textbook of Endocrinology, Philadelphia, W. B. Saunders Co. 1955, 2nd Edition, pps. 179-180.

59. Bell, G. O.: Hyperthyroidism, pregnancy and thiouracil drugs, J. A. M. A. 144:1243 1950.

60. Bothe, F. A.: Hyperthyroidism associated with pregnancy, Am. J. Surg. 101:422 1935.

61. Ficarra, B. J.: The use and abuse of the antithyroid drugs, New York State J. Med. 49:1055 1949.

62. Greenhill, J. P.: Obstetrics, Philadelphia and London, W. B. Saunders Company, 1955, Ed.II, pps. 133-134.

63. Heinemann, M., Johnson, C. E., and Man, E. B.: Serum precipitable iodine condentrations during pregnancy, J. Clin. Investigation 27:91 1948.

64. Williams, R. H., and Clute, H. M.: Thiouracil in the treatment of thyrotoxicosis, J. A. M.A. 128:65 1945.

65. Beck, B. V.: Beitr. Z. Klin. Chir. 80:73 1921. Quoted from #170.

66. Boys, C. E.: Goitre in pregnancy, J. Michigan M. Soc. 22:511 1923.

67. Brandes, R. W.: Pregnancy complicated by thyroid disease amenable to surgical treatment, Master's thesis, University of Minnesota, Sept. 1948.

68. Ciulla, U.: Ipertiroidismo in gravidanza, Annali di Ostetricia e Ginecologia Milan 71:722 1949. Quoted from Excerpta Medica 3:379 1950.

69. Clute, H. M., and Daniels, D. H.: Hyperthyroidism and pregnancy, Am. J. M. Sc. 179:477 1930.

70. Crotti, A.: Goiter and pregnancy, American Journal of Obst. & Diseases of Women and Children 75:450 1917.

71. Crotti, A.: Thyroid and Thymus, Philadelphia and New York, Lea and Febiger, 1922, Ed. II Quoted from #64.

72. Davidson, T. E.: Pregnancy complicating hyperthyroidism with report of a case, J. Iowa M. Soc. 19:64 1929.

73. Davis, C. H.: Thyroid hypertrophy and pregnancy, J. A. M. A. 87:1004 1926.

74. Davis, G. H.: Hyperthyroidism in pregnancy, Bull. School Med. Univ. Maryland 29:1 1944.

75. Hinton, J. W.: Hyperthyroidism associated with pregnancy, Am. J. Obst. & Gyned. 20:183 1930.

76. Else, J. E.: Discussion on Mussey, J. A. M. A. 87:1012 1926.

77. Englehorn: Changes in the thyroid gland in pregnancy, Verhandl. d. deutsch. path. Gesellsch. 14:675 1911. Quoted from #66.

78. Fahrni, G. S.: Pregnancy complicating hyperthyroidism and following thyroidectomy, Canad. M. A. J. 23:645 1930.

79. Falls, F. H.: Hyperthyroidism complicating pregnancy, Am. J. Obst. & Gynec. 17:536 1929.

80. Follmer, W.: Die Bedeutung der Hyperthyreose fur Cyclus unt Schwangerschaft, Arch. Gynak. 182:281 1952. Quoted from Excerpta Medica 6:532 1953.

81. Heyd, C. G.: Discussion on Dannreuther, Am. J. Obst. & Gyned. 52:61 1946.

82. Hinton, J. W., and Lord, J. W.: Is surgery indicated in all cases of nodular goiter, toxic and nontoxic?, J. A. M. A. 129:6056 1945.

83. Hinton, J. W.: The significance of thyroid enlargement during pregnancy, Am. J. Obst. & Gynec. 13:204 1927.

84. Dailey, M. E., and Benson, R. C.: Hyperthyroidism in pregnancy, Surg, Gynec. & Obst. 94:103 1952.

85. Frazier, C. H. and Ulrich, H. R.: Pathology of the thyroid gland complicating pregnancy, Am. J. Obst. & Gynec. 24:870 1932.

86. Jackson, A. S.: Hyperthyroidism complicating pregnancy, Ann. Clin. Med. 2:303 1923.

87. Javert, C. T.: Hyperthyroidism and pregnancy, Am. J. Obst. & Gynec. 39:954 1940.

88. Joll, C.: Diseases of the Thyroid Gland, London, Heinemann, 1932. Quoted from #35.

89. Jondahl, W. H., Banner, E. A., and Howell, L. D.: Management of pregnancy complicated by toxic goiter: report of a case, Proc. Staff Meet. Mayo Clin. 24:358 1944.

90. Kibel, I.: Hyperthyroidism and pregnancy, Am. J. Obst. & Gynec. 48:553 1944.

91. Lahey, F. H.: Mortality factors in thyroid disease, New York State J. Med. 31:405 1931.

92. Lehman, J. A.: Hyperthyroidism associated with pregnancy, West. J. Surg. 41:542 1933.

93. Mayo, C. H.: Keen's Surgery, Vol. 8. Quoted from #66.

94. Mengert, W. F.: Postgraduate Obstetrics, New York, P. B. Hoeber, Inc. 1947, p. 82.

95. Mussey, R. D., Plummer, W. A., and Boothby, W. M.: Pregnancy complicating exopthalmic goiter, J. A. M. A. 87:1009 1926.

96. Mussey, R. D., and Plummer, W. A.: Treatment of goiter complicating pregnancy, J. A. M. A. 97:602 1931.

97. Mussey, R. D.: The thyroid gland and the functions of reproduction, J. Michigan M. Soc. 38:295 1939.

98. Mussey, R. D., Haines, S. F., and Ward, E.: Hyperthyroidism and pregnancy, Am. J. Obst. & Gynec. 55:609 1948.

99. Falls, F. H.: Discussion on: Mussey, R. D., Haines, S. F., and Ward, E.: Am. J. Obst. & Gynec. 55:609 1948.

100. Polome, D.: Thyroidectomy late in pregnancy: report of a successful case, J. A. M. A. 99:2180 1932.

101. Portis, B., and Roth, H. A.: The diagnosis and treatment of hyperthyroidism associated with pregnancy, J. A. M. A. 113:895 1939.

102. Mussey, R. D.: Discussion on : Portis, B., and Roth, H. A.: J. A. M. A. 113: 895 1939.

103. Randall, L. M.: The thyroid gland in pregnancy, Proc. Am. Cong. Obst. & Gynec. 1:3 1939.

104. Reycraft, J. L.: The thyroid in pregnancy, Ohio State M. J. 26:759 1930.

105. Schmauch, G.: Die Schildruse der frau und ihr einfluss auf menstruation and schwaugerschaft, Menatschr. f. Geburtsh. u. Gynak. 38:662 1913. Quoted from #66.

106. Seitz, L.: Tr. Deut. Ges. f. Gynak. 1:213 1913. Quoted from #120.

107. Seitz, L.: Die Storungen der inneren Sekretion in ihren Beziehungen zu Schwangerschaft, Geburt und Wochenbett, Verhandl. d. Deutsch. Gesellsch. f. Gynak. 15:213 1913.

108. Stander, H. J.: William's Obstetrics, New York, D. Appleton-Century Co. 1935, p. 225. Quoted from #26.

109. Stander, H. J.: William's Obstetrics, New York, D. Appleton-Century Co. 1941, pps. 576-577.

110. Stepto, R. D.: Thyrotoxicosis and pregnancy, West. J. Surg. 54:317 1946.

111. Stowe, H. M.: Hyperthyroidism in pregnancy, Am. J. Obst. & Dis. Women and Children 59:789 1909.

112. Wallace, J. T.: Thyrotoxicosis and its relation to pregnancy, Am. J. Obst. & Gynec, 26:77 1933.

113. Wallace, J. T.: Thyrotoxicosis in pregnancy, M. Times, New York 68:274 1940.

114. Wernicke, G. R.: Hipertiroidismo y embarazo, La Prensa Medica Argentina 35:2140 1948. Quoted from Excerpta Medica 2:287 1949.

115. Williamson, A. C.: Pregnancy following thyroidectomy, Am. J. of Obst. & Gynec. 14:196 1927.

116. Yoakam, W. A.: The thyroid gland in pregnancy: a clinical study in a region of endemic goiter, Am. J. Obst. & Gynec. 15:617 1928.

117. Astwood, E. B.: Chemotherapy in hyperthyroidism, Surgery 16:670 1944.

118. Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil, J. A. M. A. 122:78 1943.

119. Ballantyne, J. W.: Manual of Antenatal Pathology, p. 116. Quoted from #161.

120. Bartels, E. C.: Propylthiouracil: its use in the preoperative treatment of severe complicated hyperthyroidism, West. J. Surg. 56:226 1948.

121. Kosmok: Monograms on Toxemias of Pregnancy, New York, Appleton and Co. Quoted from #66.

122. von Beck, B.: Struma and Schwangerschaft, Beitr. z. Klin. Chir. 80:73 1912. Quoted from #42.

123. Berry, J.: Diseases of the Thyroid Gland and Their Surgical Treatment, p. 45. Quoted from #161.

124. Bielschowsky, F.: Tumors of the thyroid produced by 2-acetyl-aminofluorene and allylthiourea, Brit. J. Exper. Path. 25:90 1944.

125. Kraus, H.: Thyroid function during pregnancy, Arch. f. Gynak. 126:1 1924. Quoted from #163.

126. Bokelmann, O., and Scheringer, W.: Beitrag zur Kenntnis der Schilddrusenfunktion und des Jodstoffwechsels in der Gestation, Arch. f. Gynak. 143:512 1931. Quoted from # 2.

127. Bonnaire: Presse Med. 1910. Quoted from #86.

128. Bram, I.: Graves' disease and pregnancy, Pennsylvania M. J. 39:239 1936.

129. McLaughlin, C. W., Jr., and McGoogan, L. S.: Hyperthyroidism complicating pregnancy, Am. J. Obst. & Gynec. 45:591 1943.

130. Ward, G. G., Jr.: The relation of the thyroid gland and thyroidism to the toxemia of pregnancy, Tr. Am. Gynec. Soc. 34:766 1909.

131. Colvin, E. D. and Bartholomew, R. A.: Behavior of the basal metabolism in the course of developing toxemia of pregnancy: correlation with cholesterol, placental infarctions and retinal examination, Am. J. Obst. & Gynec. 37:584 1939.

132. Babcock, W. W.: Discussion on Colvin, E. D., and Bartholomew, R. A., Am. J. Obst. & Gynec. 37:584 1939.

133. Curtis, G. M., and Swenson, R. E.: Thiouracil and its allies in the treatment of hyperthyroidism, Surg., Gynec. & Obst. Int. Abst. of Surg. 86:105 1948.

134. Daly, P. A., and Strouse, S.: The thyroid during pregnancy, J. A. M. A. 84:1798 1925.

135. Eason, J.: The correlations of graves' disease and thyroiditis, Edinburgh M. J. 35:169 1928.

136. Edgar: Obstetrics, Quoted from #239.

137. Fruhinsholz, A., and Parisot, J.: Des anomaties de la fonction thyroidienne dans leurs rapports avec la gestation, Ginecologia XX:611 1921.

138. Gardiner-Hill, H.: Pregnancy complicating simple goitre and graves' disease, Lancet 1:120 1929.

139. Ganigues: Obstetrics. Quoted from #239.

140. Halliday-Croom: Tr. Edinburgh Obst. Soc. XXX:143 Quoted from #239.

141. Halliday-Crpom, S. J.: Exophthalmic goitre in its relation to gynaecology and obstetrics, J. Obst. & Gynec. Brit. Emp. 11:368 1907.

142. Hertzler, A. E.: Pathogenesis of goiter considered as one continuous disease process, Arch. Surg. 16:61 1928.

143. Hiilesmaa, V. A.: Studies of the thyroid gland of patients and newborn infants in southern Finland, Acta Obst. et Gynec. Scandinav. 28:1 1948.

144. Garcia Gallego, J.: Hipertiroidismo de la lactancia, Med. Espan. 17:477 1947.

145. McGavack, T. H.: The Thyroid, St. Louis, C. V. Mosby., 1951, pp. 218-228.

146. Mitskevich, M. S.: Changes in thyroid of embryo guinea pigs after action of methylthiouracil on pregnant females, Doklady Akad. Nauk S. S. S. R. 60:325 1948. Quoted from Chem. Abstr. 42:6460 1948.

147. Schilddruse, J.: Handbuch d. speziellen pathologischen anatomie und Histologie, Berlin, Julius Springer, 1926, Bd. 8. Quoted from #145.

148. Windle, W. F.: Physiology of the Foetus: Origin and Extent of Function in Prenatal Life, Philadelphia, W. B. Saunders Co., 1940 p. 197. Quoted from #55.

149. Hyman, H. T., and Kessel, L. J.: Studies of exophthalmic goiter and the involuntary nervous system, J. A. M. A. 88:2032 1927.

150. Kleinwachter: Quoted from #86.

151. Kleinwachter: Quoted from #72.

152. Lange: Leitschr. f. Geburt. u. Gyn. 40:34 1899.

153. Lichtenstein: Progressive Medicine III:168 1909. Quoted from #197.

154. Mackenzie: Albutt's System of Medicine, Vol. IV Part 1, p. 361. Quoted from #239.

155. Marhoe, J. W.: Discussion on #165. J. A. M. A. 71:877 1918.

156. Mussey, R. D.: The thyroid gland and pregnancy, Am. J. Obst. & Gyned. 36:529 1938.

157. Nicholson: Scottish Med. Surg. J. 6:503 1901. Quoted from #130.

158. Nicholson: Scottish Med. Surg. J. 6:503 1901. Quoted from # 239.

159. Plass, E. D., and Yoakam, W. A.: Basal Metabolism studies in normal pregnant women with normal and pathologic thyroid, Am. J. Obst. & Gynec. 18:556 1929.

160. Plummer, H. S., and Boothby, W. M.: The value of iodine in exophthalmic goiter, J. Iowa M. Soc. 14:66 1924.

161. Rhind, S. D.: The treatment of hyperthyroidism during pregnancy, New Zealand M. J. 32:34 1933.

162. Meyer, L: Quoted from #42.

163. Stewart, J. D. and Menne, F. R.: The relationship of iodine to the basal metabolic rate and to the changes in the thyroid gland in pregnant rabbits--an experimental study, Endocrinology 17:93 1933.

164. Stockl, E.: Schwangerschafts und Geburtsverlauf bei Basedowscher Krankheit und Struma, Leitschrift fur Geburtshulfe und Gynakologie, 129:286 1948. Quoted from Excerpta Medica 2:248 1949.

165. Watson, L. F.: Goiter in Pregnancy, J. A. M. A. 71:875 1918.

166. Zener, F. B., David, N. A., and Phatak, N. H.: The effect of iodine therapy on the blood iodine and basal metabolic rate during pregnancy, West. J. Surg. 55:375 1949.

167. Wilson, R. R.: Effects of thyroid activity on female organism, Northwest Med. 29:425 1930.

168. Norrman, E.: Strumektomie in der Graviditat, Acta chir. Scandinav. 88:526 1943.

169. Means, J. H.: The Thyroid and its Diseases, Philadelphia, J. B. Lippincott Co., 1948, 2nd Edit. p. 437.

170. Fleischer, A. J.: Thyrotoxicosis complicated by pregnancy, Am. J. Obst. & Gynec. 22:273 1931.

171. Brain, I.: Thiouracil in the conservative treatment of exophthalmic goiter, Med. Rec. 158:416 1945.

172. Rose, E. and McConnell, J.: Thiouracil in the treatment of thyrotoxicosis, Am. J. M. Sc. 208:561 1944.

173. Williams, R. H., Clute, H. M., Anglem,T. J., Kenney, F. R.: Thiouracil treatment of thyrotoxicosis, J. Clin. Endocrinol. 6:23 1946.

174. Van Winkle, W. V., Jr., Hardy, S. M., Hazel, G. R., Hines, D. C., Newcomer, H. S., Sharp, E. A., and Sisk, W. M.; The clinical toxicity of thiouracil, J. A. M. A. 130:343 1946.

175. Williams, Weinglass, Bissell, and Peters: Anatomical effects of thiouracil, Endocrinology 34:317 1944.

176. Money, W. L.: The effects of chronic treatment on the thyroid gland of the white race, Anat. Rec. 96:544 1946.

177. Stanley, M. M., and Astwood, E. B.: 1-Methyl -2-mercaptoimidazole: an antithyroid compound highly active in man, Endocrinology 44:588 1949.

178. Williams, R. H. and Bissell, G. W.: Thiouracil in the treatment of thyrotoxicosis, New England J. Med. 229:97 1943.

179. Physician's Bulletin: Thyroid disease, 20:131 1955.

180. Bartels, E. C.: Hyperthyroidism--an evaluation of treatment with antithyroid drugs followed by subtotal thyroidectomy, Ann. Int. Med. 37:1123 1952.

181. Livingstone, H. J., and Livingstone, S. F.: Agranulocytosis and hepatocellalar jaundice; toxic reactions following propylthiouracil therapy, J. A. M. A. 135:422 1947.

182. Juliar, B., and Harric, T. L.: Fatal agranulobytosis occurring during propylthiouracil therapy; report of a case, J. A. M. A. 139:646 1949.

183. Beebe, R. T., Propp, S., McClintoch, J. C., and Versaci, A.: Fatal agranulocytosis during treatment of toxic goiter with propylthiouracil, Ann. Int. Med. 34:1035 1951.

184. Colwell, A. R., Jr., Sando, D. E., and Lang, S. J.: Propylthiouracil induced agranulocytosis, toxic hepatitis and death, J. A. M. A. 148:639 1952.

185. Doederlein, G.: Arch. f. Gynak 155:22 1934. Quoted from #194.

186. Freiesleben, E., and Kjerulf-Jensen, K.: The effect of thiouracil derivatives on fetuses and infants, J. Clin. Endocrinol. 7:47 1947.

187. Peterson, R. R., and Yound, W. C.: The problem of placental permeability for thyrotrophin propylthiouracil and thyroxine in the guinea pig, Endocrinology 50:218 1952.

188. Schittenhelm, A., and Eisler, B.: Ztschr. f. d. ges. exper. Med. 95:124 1935. Quoted from #194.

189. Williams, R. H., Kay, G. A., and Jandorf, B. F.: Thiouracil; its absorption, distribution and excretion, J. Clin. Invest. 23:603 1944.

190. Aron, M.: Compt. Rend. Soc. de biol. 102:683 1929. Quoted from #194.

191. Williams, R. H. and Kay, G. A.: Thiouracils and thioureas, Arch. Int. Med. 80:37 1947.

192. Dorff, G. B.: Sporadic cretinism in one of twins, Am. J. Dis. Child. 48:1316 1934.

193. Grumbrecht, P., and Loeser, A.: Klin. Wchnschr. 17:233 1938. Quoted from #194.

194. Whiteside, B.: The effect of thyrotropic hormone upon pregnant rabbits, Endocrinology 26:136 1940.

195. Williams, R. H.: Further studies of the absorption distribution, and elimination of thiouracil, J. Clin, Endocrinol. 4:385 1944.

196. Davis, C. H.: The propylatic treatment of thyroid dysfunction and the importance of blood metabolism studies in obstetrics and gynecology, Am. J. Obst. & Gynec. 24:607 1932.

197. Porter, M. F.: Diseases of the thyroid in the female, Am. J. Obst. and Dis. of Women and Child. 64:781 1911.

198. Ripmann: Quoted from # 253.

199. Rubsamen, W.: Ueber Schilddrusenerkrankungen in der schwangerschaft, Arch. f. Gynak. 98:268 1912. Quoted from #145.

200. Van Graff, E.: Arch. f. Gynak. cii:18 1914. Quoted from #253.

201. Freund: Inaug. Dissert., Strassburg, 1882. Quoted from #130.

202. Dock, G.: Diseases of thyroid, Osler and McCrae's Modern Medicine, 5:339 1927. Quoted from #138.

203. Phatak, N. M., Zener, F. B., and David, N. A.: Effects of iodine therapy on blood iodine and basal metabolism rate in pregnancy, Proc. Soc. Exper. Biol. & Med. 45:667 1940.

204. Zuntz, L.: Arch. f. Gynak. xc:452 1910. Quoted from #225.

205. Maurer, E. E.: Arch. f. Gynak. 130:70 1927. Quoted from #166.

206. Winfield, P.: Minutenvolumen und respiratorische Stoffwechselbestimmungen wahrend der graviditat, Acta Obstet. et Gynec. Scand. 10:182 1930.

207. Wilson, C. M. and Bourne, A. W.: On the relation of the thyroid gland to the female pelvic organs, Lancet 1:1038 1922.

208. Stander, H. J., and Peckham, C. H.: Basal metabolism in the toxemias of pregnancy, Bull. Johns Hopkins Hosp. 38:227 1926.

209. Sandiford, I., Wheeler, T., and Boothby, W.: Metabolic studies during pregnancy and menstruation, Am. J. Physiol, 96:191 1931.

210. Sandiford, I., and Wheeler, T.: The basal metabolism before, during and after pregnancy, J. Biol. Chem. 62:329 1924.

211. Root, H. F., Root, H. K.: The basal metabolism during pregnancy and the puerperium, Arch. int. Med. 32:411 1923.

212. Pommerenke, W. T., Haney, H. F., Meek, W. J.: Energy metabolism of pregnant rabbits, Am. J. Physiol. 93:249 1930.

213. Plass, E. D. and Yoakum, W. A.: Basal metabolism studies in normal pregnant women with normal and pathologic thyroid glands, Tr. Am. Gynec. Soc. 54:165 1930.

214. Murlin: The metabolism of development, Am. J. Physiol. 26:134 1910.

215. Marine, D., Cipra, A., and Hunt, L.: Influence of the thyroid gland on the increased heat production occurring during pregnancy and lactation, M. Metab. Research 5:277 1924.

216. Magnus-Levy, H.: Leitschr. f. Geburt. U. Gynak. Lii:116 1904. Quoted from #225.

217. Hughes, E. C.: A study of 1,250 basal metabolisms during pregnancy, New York State J. Med. 34:873 1934.

218. Hasselbach, K. A.: Skand. Arch. Physiol. xxvii:1 1912. Quoted from #222.

219. Hanna, B. C.: The basal metabolic rate in normal pregnancy, Am. J. Obst. & Gynec. 35:155 1938.

220. Cornell, H. L.: Metabolism readings in 84 pregnant cases, Surg., Gynec. & Obst. 36:53 1923.

221. Carpenter, T. M., and Murlin, J. R.: The energy metabolism of mother and child just before and just after birth, Arch. Int. Med. 7:184 1911.

222. Baer, J. L.: Basal metabolism in pregnancy and the puerperium, Am. J. Obst. & Gyned. 2:249 1921.

223. Magnus-Levy, H.: 1897. Quoted from #166.

224. Rowe, A. W., and Boyd, W. C.: The metabolism in pregnancy, J. Nutrition 5:551 1932.

225. Harding, V. J.: Metabolism in pregnancy, Physiol. Rev. 5:279 1925.

226. Gardner, J. A., and Gainsborough, H.: The cholesterol metabolism during pregnancy, Lancet 1:603 1929.

227. Boyd, E. M.: The lipemia of pregnancy, J. Clin. Investigation 13:347 1934.

228. Anselmino, K. J., and Hoffman, F.: Arch. f. Gynak. 145:95 1931. Quoted from #15.

229. Man, E. B., Smirnow, A. E., Gildea, E. F., and Peters, J. P.: Serum iodine fractions in hyperthyroidism, J. Clin. Investigation 21:773 1942.

230. Peters, J. P., Man, E. B., and Heinemann, M.: Pregnancy and the thyroid gland, Yale J. Biol. & Med. 20:449 1948.

231. Man, E. B., Heinemann, M., Johnson, C. E., Leary, D. C., and Peters, J. P.: The precipitable iodine of serum in normal pregnancy and its relation to abortions, J. Clin. Investigation 30:137 1951.

232. Engstrom, W. W., Markardt, B., and Liebman, A.: Effect of estrogen on serum precipitable iodine, Proc. Soc. Exper. Biol. & Med. 81:582 1952.

233. Engstrom, W. W., Kydd, D. M., Peters, J. P., and Man, E. B.: The precipitable iodine of serum in pregnancy complicated by disorders of the thyroid, J. Clin. Investigation 30:151 1951.

234. Davis, C. H.: Discussion of Mussey, R. D. and Plummer, W. A. in #96.

235. Graham, A.: Exopthalmic goiter and toxic adenoma, J. A. M. A. 87:628 1926.

236. Falls, F. H.: Observations in the use of Lugol's solution in hyperemesis gravidaius, Am. J. Obst. & Gyned. 22:882 1931.

237. Rutherford, R. N.: The use of thiourea and thiouracil in pregnancy, West. J. Surg. Obst. & Gynec. 54:7 1946.

238. Soule, S. D.: A study of thyroid activity in normal pregnancy, Am. J. Obst. & Gyned. 23:165 1932.

239. White, C.: Exppthalmic goitre and pregnancy labour and the puerperium, J. Obst. & Gynaec. Brit. Emp. 20:126 1911.

240. Gellhorn, G.: Exophthalmic goiter and pregnancy, Am. J. Obst. & Dis. of Women & Child. 68:1132 1913.

241. Joll, C. A.: Diseases of the Thyroid Gland, St. Louis, The C. V. Mosby Company, 1940, pp.439-441 & p. 522.

242. Williams, W.: Obstetrics, New York. Quoted from #71.

243. Williams, W.: Obstetrics, New York. Quoted from #259.

244. Dannreuther, W. T.: Therapeutic abortion in a general hospital, Am. J. Obst. Gynec. 52:54 1946.

245. Chesky, V. E., Schmidt. C. R. and Walsh, W. R.: Liver damage in thyroid disease, West. J. Surg. 49:499 1941.

246. Ward, G. G. : The relation of the thyroid gland and thyroidism to the toxaemia of pregnancy, Surg., Gynec. & Obst. 9:617 1909.

247. Stoeckl, E.: Schwangerschafts und Geburtsverlauf bei basedowscher Krankheit und Struma, Ztschr. Geburtsh. 129:286 1948. Quoted from #84.

248. Theilhaber: Arch. f. Gynaec., Berlin, 1895, bd. xlix, heft I, p. 57. Quoted from #130.

249. Vorzeimer, J. J., Fishberg, A. M., Langrock, E. G. and Rappaport, E. M.: The endocrine basis of toxemia of pregnancy, Am. J. Obst. & Gynec. 33:801 1937.

250. White, C.: A foetus with congenital hereditary graves' disease, J. Obst. & Gynaec. Brit. Emp. 21:231 1912.

251. Kunde, M. M., Carlson, A. J., and Proud, T.: The ovary in experimental hypo- and hyper-thyroidism, Am. J. Physiol. 88:747 1929.

252. Seitz, L.: Arch. f. Gynak. 137:608 1929. Quoted from #254.

253. Robinson, A. L.: Hyperthyroidism in pregnancy, J. Obst. & Gynaec. Brit. Emp. 29:296 1922.

254. Chapman, E. M., Corner, G. W., Jr., Robinson, D., and Evans, R. D.: The collection of radioactive iodine by the human fetal thyroid, J. Clin. Endocrinol. 8:717 1948.

255. Ott,I.: Textbook of Physiology, 1909, p.403. Quoted from Fenger, F.: J. Biol. Chem. 14:397 1913.

256. Grollman, A.: Essentials of Endocrinology, Philadelphia, J. B. Lippincott Co., 1947, p. 155. Quoted by #53.

257. Nurnberger, C. E., and Lipscomb, A.: Transmission of radioiodine I^{131} to infants through human maternal milk, J. A. M. A. 150:1398.

258. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Co., 1937, p. 602. Quoted from #55.

259. Soley, M. H., and Stone, R. S.: Roetgenray treatment of hyperthyroidism, Arch. Int. Med. 70:1002 1942.