HYPERTHYROIDISM IN PREGNANCY: A STUDY OF 37 PREGNANCIES IN 34 PATIENTS

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SYNOPSIS

Over a $3\frac{1}{2}$ year period 37 pregnancies in 34 patients were studied. The mean age was 29·5 years; 75·7% of the patients were para 3 or less. The incidence of hyperthyroidism in pregnancy was 0·1%. In 20 pregnancies antithyroid drug was given (nonthyroxine group) while in 17 pregnancies antithyroid drug and thyroxine were given (thyroxine group). The incidence of toxaemia of pregnancy was significantly higher (2·3 times higher) in the thyroxine group. There was a foetal loss (2·7%) from prematurity. This single foetal loss occurred in the thyroxine group. The remaining 36 babies were healthy and there was no congenital abnormality, neonatal goiter or thyroid dysfunction. Thyroxine appears to confer no advantage in the treatment of hyperthyroidism in pregnancy and appears to be harmful as the incidence to toxaemia of pregnancy is increased. It is concluded that hyperthyroidism in pregnancy should be treated with antithyroid drug alone.

Hyperthyroidism is occasionally associated with pregnancy. The association is of importance because uncontrolled hyperthyroidism can be a major hazard for the pregnant woman and her fetus. Conflicting opinions have been expressed concerning the effect of hyperthyroidism on pregnancy and the appropriate treatment of hyperthyroidism occurring during pregnancy. The purpose of this paper is to discuss certain of these controversial issues and to review the experience in the University Unit, Kandang Kerbau Hospital during the past $3\frac{1}{2}$ years.

MATERIAL

From January 1968 to June 1971, there were 37 pregnancies occurring in 34 hyperthyroid patients. The total number of deliveries during the period under review was 37,568 .Of the 34 patients, there were 30 Chinese, 3 Malays and one Indian. All the patients had diffuse toxic goitre. Eight of the 34 patients experienced the onset of thyrotoxic symptoms during pregnancy; 4 during the 1st trimester, 2 in the 2nd trimester and 2 in the 3rd trimester. The thyroid status at conception was not known. Symptoms antedated the pregnancy in 26 patients.

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All the patients were treated medically and there are 2 regimes of treatment.

In one group of 20 pregnancies, the patients were treated with antithyroid drugs; 19 were treated with carbimazole and the remaining one with propylthiouracil. The patients were treated with a high initial dose (40 to 60 mg. daily). When subjective and objective improvements were made, the dose was reduced progressively until a maintenance dose was reached (5 to 15 mg. daily). The drugs were taken off in the last trimester if patient remained euthyroid. This group is referred to in the rest of the text as the nonthyroxine group. In another group of patients with 17 pregnancies, L-thyroxine in a dosage of 0·1-0·3 mg. daily was added to the treatment once the maintenance dose of antithyroid drug was reached and the combined thyroid-antithyroid therapy was continued till delivery. This second group is referred to in the rest of the text as the thyroxine group. The two groups were comparable in age and parity.

RESULTS

Incidence

At the University department of Obstetrics and Gynaecology, Kandang Kerbau Hospital, Singapore the incidence of hyperthyroidism during pregnancy is 0·1% or one in 1,000 pregnancies.

The age of the patient at the time of consultation is shown in Table I.

The age range was from 20 to 39 years. The average age was 29·5 years. 84·2% of the cases were in the age group 25-35 years.

Age

TABLE I

AGE OF THE PATIENTS

Age in Years	No. of Patients
20 - 24	2
25 - 29	19
30 - 34	12
35 and above	4
TOTAL	37

Parity

TABLE II

PARITY OF PATIENTS

Parity	No. of Patients
0 - 1	16
2 - 3	12
4 - 5	7
6 and above	2
TOTAL	37

The parity of the patients is shown in Table II. The number of patients decreased with increasing parity, 75·7% of the patients were para three or less.

Laboratory Investigations

Of the patients studied, the protein bound iodine values ranged from 6·8 to 16 microgrammes per cent with a mean of 12·5 microgrammes per cent. The normal range in pregnant patient is from 6 to 11 microgrammes per cent (Peters, 1948).

The basal metabolic rate (Du Bois) ranged from +23% to +78% with a mean value of +49%. In normal pregnant woman, the peak basal metabolic rate is + 20%. Of the 8 patients in whom diagnosis of hyperthyroidism was made during pregnancy, only one patient had a protein bound iodine value of 6·8 microgrammes%; the remaining 7 patients had a value of 11 microgrammes per cent and above. All the patients with the B.M.R. done had a value in excess of + 20 %.

Maternal Complications

Hypertensive disorders of pregnancy was diagnosed when the patient, above 20 weeks gestation and within two weeks postpartum was found to have a blood pressure of $\frac{130}{90}$ mm.Hg. and above and with or without proteinuria and/or ankle oedema. They were arbitarily divided into 3 groups: Mild (diastolic pressure of 90-99 mm.Hg.); moderate (diastolic pressure of 100-109 mm.Hg.) and severe (diastolic pressure of 110 mm.Hg. and above).

In our series, fifteen pregnancies were complicated by hypertension, an incidence of 40·6 per cent. The incidence of hypertensive disorders of pregnancy in the general obstetric population in our unit is 7·1%. Of the fifteen cases, 8 were classified as mild 4 were moderate and 3 were severe.

Three patients were investigated for infertility before the present pregnancy. Two patients gave a history of having had repeated abortions and premature labours before they were investigated.

Perinatal Mortality

A total of 37 pregnancies occurred in 34 patients with hyperthyroidism. Thirty-seven living babies were produced. There was one fetal loss during the neonatal period. The mother was first seen at 16 weeks gestation when hyperthyroidism was detected. Carbimazole and L-thyroxine were administered. However, her hyperthyroidism was not well under control. At 30 weeks of gestation she went into premature labour, delivering a feeble baby which died from prematurity. This represents a fetal loss of 2·7 per cent in this series.

There were 5 premature babies weighing 5 lb. or less out of the total of 37. The prematurity rate was 13·5 per cent. Out of the 5 prematures, 2 belonged to the thyroxine group while the remaining 3 were in the nonthyroxine group. All the babies were under the close supervision of the paediatrician after delivery. They were discharged from the nursery after few days when they were found in satisfactory condition. Except for the neonatal death, all babies including the premature ones had developed normally. There were no congenital abnormalities, no neonatal goitres or other thyroid complications.

Birthweight

TABLE III

BIRTHWEIGHT OF THE BABIES IN THE NONTHYROXINE AND THYROXINE GROUPS

	Nonthyroxine	Thyroxine
2000 Gm.	—	1
2000 - 2499 gm.	4	5
2500 - 2999 gm.	8	3
3000 - 3499 gm.	8	7
3500 and above	—	1
TOTAL	20	17

The average birthweight of the babies in the nonthyroxine and the thyroxine groups were 2820 ± 501G (2SD) and 2762 ± 546G (2SD) respectively. The difference between the 2 means was statistically significant ($P<0.05$).

Further breakdown of the 17 pregnancies in the thyroxine group showed that the average birthweight of the 10 pregnancies complicated by hypertension was 2701 gm. and that of the 7 uncomplicated pregnancies was 2824 gm.

Onset of Therapy

Of the 20 patients in the nonthyroxine group only one patient was treated in the 3rd trimester. The remaining 19 were treated in the 1st trimester. In the thyroxine group, 14 patients were given treatment in the 1st trimester, two in the 2nd and one in the last trimester. The number of patients treated in the last 2 trimesters was too small for the evaluation of effect of therapy in relation to the onset of therapy.

Hypertensive Disorder of Pregnancy and Methods of Therapy

TABLE IV

HYPERTENSIVE DISORDERS OF PREGNANCY IN THE NONTHYROXINE AND THYROXINE GROUPS

	Non-thyroxine	Thy-roxine	Total
Hypertension	5	10	15
No hypertension	15	7	22
TOTAL	20	17	37

The relationship between methods of therapy and patients who were hypertensive is shown in Table IV.

In the nonthyroxine group 25% of pregnancies were complicated by hypertension during pregnancy; whilst 58·8% of pregnancies in the thyroxine group were complicated by the same condition. The incidence of toxaemia in the thyroxine group was 2·3 times higher than the nonthyroxine group and the difference is statistically significant ($P<0.05$).

DISCUSSION

The incidence of hyperthyroidism in pregnancy is reported to vary from 0·22 to 3·7% with an average of about 0·2% (Becker and Sudduth, 1959; Mussey *et al*, 1948). The incidence of hyperthyroidism in this series is 0·1%.

Pregnancy is associated with significant alterations in thyroid function and diagnosis of thyrotoxicosis during pregnancy often offers a challenge to the clinician. During normal pregnancy, the thyroid gland typically undergoes hypertrophy and goitre may be present clinically. In fact, Crooks *et al* in 1962 reported an incidence of 70% of goitre during pregnancy. Tachycardia, tremor, skin warmth, heat intolerance and emotional instability are present in many normal pregnant women and when goitre is found in addition to these symptoms, a diagnosis of hyperthyroidism may be made too readily. The diagnosis of hyperthyroidism in pregnancy is usually based on clinical manifestations because laboratory tests are less reliable under these circumstances. Hyperthyroidism usually induces further increases in the basal metabolic rate and protein bound iodine above normal pregnancy values. However, provided one remembers the higher range of normal figures during pregnancy, these tests are helpful in clarifying the diagnosis.

Hyperthyroidism in pregnancy is said to be associated with a higher incidence of hypertension than in routine obstetrics practice. Javert (1940) reported an incidence of hypertension of pregnancy associated with hyperthyroidism of 77% at the New York Hospital. In this series, the incidence of toxaemia of pregnancy is 40·6%, a 6 fold increase over the general population. Another interesting finding emerged from this study. In analysing incidence of hypertension in patients treated by the 2 regimes, it was found that the incidence of hypertension in the thyroxine group was 2·3 times higher than in the nonthyroxine group. The difference is statistically significant ($P<0.05$).

It has also been suggested that hyperthyroidism is accompanied by an unusually higher incidence of abortion and premature births. Of the 37 pregnancies in our series, none ended in spontaneous abortion, but 5 premature births occurred. The prematurity rate is 13·5% which is about 3 times higher than the incidence in our hospital population.

Herbst and Selankow (1965) treated 24 patient with thyroxine and antithyroid drugs through 32 pregnancies. The pregnancy loss was 9·4 per cent. In our series of 17 patients received antithyroid drug and thyroxine there was 1 pregnancy loss or 5·8%. There was no fetal loss in the group of patients treated with antithyroid drug alone.

Burrow (1965) in a study of 41 pregnancies in 30 women in whom antithyroid drugs alone were used, found that there were 5 (13·5%) goitrous infant, and 4 (10%) abnormal offspring (hypothyroidism, mongolism, hyperthyroidism and cryp-

torchism). All the infants in our series were delivered normally and free from thyroid complications.

Results obtained from drug treatment of hyperthyroidism in pregnancy vary considerably. Astwood (1951) followed up 22 pregnancies in patients on antithyroid drugs. Twenty-two living children resulted and there was no evidence of thyroid disturbance or goitre in the newborn children. The dosage was reduced as pregnancy progressed and the treatment was stopped by the eighth month. This would minimise the risk of inducing fetal goitre. However, reports of high fetal losses and neonatal complications e.g. goitre and cretinisms subsequently appeared in the literature. Piper and Rosen (1954) reported 11 pregnancy losses out of 16 cases following antithyroid medication, which was discontinued in the 6th or 7th month of pregnancy. Becker and Sudduth (1959) reported one cretin and also one neonatal death due to a large goitre in their series of 22 pregnancies in thyrotoxic women.

The combined use of antithyroid drugs and thyroid hormones for the treatment of hyperthyroidism and pregnancy was then advocated. (Herbst and Selenkow, 1965). Both the mother and foetus are said to be protected against the deleterious effects of hypothyroidism and its complication. Increase in size of the thyroid gland beyond that already present in the mother and the development of goitre in the infant are prevented. Management of hyperthyroidism is simplified since it is not necessary to obtain the precise dose of antithyroid drug that will just control hyperthyroidism and does not cause hypothyroidism in mother or fetus. In the series reported by Herbst and Selenkow (1965) the fetal loss was 9·4% which compared favourably with 8·8% in nondiabetic women at the same hospital during the same period.

In our series of 37 pregnancies in 34 patients, the results of medical treatment were on the whole encouraging. The gross fetal loss wse 2·7 per cent corrected to 0 per cent by deducting the premature infant in a patient with uncontrolled hyperthyroidism. Provided the mother was not overtreated and made hypothyroid, the pregnancy can be managed by antithyroid drugs. There were no undue risks both to the mother and to the infant. There is no advantage in adding thyroxine as there wse a fetal loss from prematurity in the thyroxine group and there was no fetal loss in the nonthyroxine group. All the babies (other than the fetal loss) were healthy and free from neonatal goiter and thyroid dysfunction. In fact the use of thyroxine appears to be harmful as in our series the incidence of toxaemia is increased significantly in the thyroxine group. The use of thyroxine is theoretically unsound as it is now known that while antithyroid drug crosses the placenta freely, thyroxine moves across only slowly (Means, De Groot and Stanbury, 1963). We cautiously concluded, as the number in our series is relatively small, that hyperthyroidism in pregnancy, should be treated with antithyroid drug alone, the addition of thyroxine appears to confer no advantage and is in fact deleterious.

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