THYROTOXICOSIS IN PREGNANCY – A SIX YEAR REVIEW

B H Lim, S Raman, V Sivanesaratnam, A Ngan

ABSTRACT

Twenty eight patients with hyperthyroidism complicating their pregnancies were seen at the Obstetrics and Gynaecology Department, University Hospital, Kuala Lumpur, Malaysia in a six-year period. All patients were treated with antithyroid drugs, carbimazole being the mainstay of treatment. The incidence of the disease was 0.9 per 1000 births and was similar with other series. No cases of fetal goitre were noted. The mean birth weight was 2952 g; there was no significant difference in the birth weight of term live births in patients treated with carbimazole alone or cabimazole combined with propranolol.

Keywords: Hyperthyroidism, antithyroid drugs, fetal abnormality, Free Thyroxine Index, Goitre

SING MED J. 1989; NO 30: 539-541

INTRODUCTION

The subject of maternal and fetal thyroid hormone metabolism during the course of pregnancy has been under constant investigation for many years now. As it is a fairly rare condition, being reported from 0.2 (1) to 2 per 1000 (2) deliveries, there remain some controversial aspects in the optimal approach to the management of this condition viz. medical versus surgical approach and about the best form of medical therapy (1,2). Furthermore, symptoms of hyperthyroidism may sometimes be masked by the normal signs of pregnancy, leading to late diagnosis. Early diagnosis and treatment is important to minimise fetal loss which in untreated patients may be as high as 48% (3). Even in treated women, neonatal morbidity has also been reported with a 15% incidence of neonatal goitre (4) caused by transplacental passage of anti-thyroid drugs and the compensatory rise in Thyroid Stimulating Hormone (TSH) (5). A significant reduction in birthweight has also been reported (6). This has been attributed to the use of propranolol in the treatment of acute symptoms of thyrotoxicosis in pregnancy. Although propranolol has rarely been reported to cause growth retardation, hypoglycaemia, neonatal respiratory depression and prolonged labour its safety has now been established through extensive use (7,8).

Department of Obstetrics & Gynaecology
University Hospital
Kuala Lumpur
Malaysia

B H Lim, MRCOG
S Raman, MRCOG, FICS, FACS
V Sivanesaratnam, FRCOG, FICS, FACS

Subang Jaya Medical Centre
Malaysia

A Ngan, FRACP

Correspondence to: Assoc Prof Raman

The commonly used drugs in the treatment of thyrotoxicosis in pregnancy are the thionamides, propylthiouracil and carbimazole (the active component of which is methimazole).

These drugs block the glandular synthesis of thyroid hormone but propylthiouracil has the added advantage of blocking peripheral conversion of thyroxine to triiodothyronine. Both drugs cross the placenta and may block the fetal thyroid gland but studies in animal as well as human models (9) have shown that the placenta is more permeable to methimazole than to propylthiouracil.

This is a retrospective analysis to assess the outcome of all pregnancies complicated by hyperthyroidism in a six year period in a large teaching centre in Malaysia.

Materials and Methods

Twenty-eight women with thyrotoxicosis complicating their pregnancies were managed during a six year period from 1978 to the end of 1983 at the University Hospital, Kuala Lumpur, Malaysia. They were aged between 20 and 41 years (mean 29.14 years). The anti-thyroid therapy administered is detailed in Table I.

The diagnosis of thyrotoxicosis in pregnancy was based mainly on clinical grounds with the help of biochemical parameters. The Free Thyroxine Index (FTI) was used to assess thyroid secretory function. This eliminates changes due to altered TBG and is derived by the formula:

$$\frac{10 \times \text{Serum T4}}{\text{T3 Resin uptake}}$$

Patients already on treatment before conception were maintained on an average daily dose of 5 to 15 mg of carbimazole. A small dose of propranolol (20 mg tds) was added in 9 of the patients who showed overt symptoms of sympathetic over-activity. None of these patients had more than 8 weeks of propranolol therapy.

In patients diagnosed for the first time during pregnancy, carbimazole 15 mgs tds was the initial treatment which was then reduced to a maintenance dose of 5 to 15 mg daily after 6 to 8 weeks. The

Table I
DRUGS USED IN THE TREATMENT OF THYROTOXICOSIS IN PREGNANCY IN TWENTY EIGHT PATIENTS FROM 1978 TO 1983.

Drug	Before Conception	After Conception	No. of Patients
Carbimazole	8	5	13
Carbimazole + L – Thyroxine	4	2	6
Carbimazole + Propranolol	5	1	6
Carbimazole + Propranolol + L – Thyroxine	3	0	3
Total	20	8	28

response to treatment was monitored clinically and biochemically. Treatment was stopped between 36 weeks and delivery.

Patients were managed jointly by the Obstetrician and Endocrinologist. The newborns were assessed by the Paediatrician and admitted to the Special Care Nursery where biochemical evaluation of thyroid status was performed if there was clinical suspicion of thyroid dysfunction.

Statistical analysis was done by the Student's t test.

RESULTS

Twenty eight singleton pregnancies were studied. Eight patients were diagnosed to have hyperthyroidism during pregnancy, two of whom were booked during the 3rd trimester. During the study period there were 32,380 deliveries, making the incidence 0.9 per 1000 deliveries.

Racial Distribution

The Chinese group of patients made up 53% of the total. The Malays made up 7 (25%) and Indians 5 (17.9%) of the total. There was one patient (3.5%) who was an Orang Asli. This did not differ from the racial breakdown in the antenatal clinical attendance at the hospital during the period of study.

Onset of Labour

There were 5 preterm deliveries. One was an emergency caesarean section for antepartum haemorrhage while 4 (14.3%) were spontaneous preterm labours. This is higher than the quoted incidence of 6% (9) but as all these 4 patients were euthyroid at the time of delivery, the onset of labour could not be attributed to the disease itself.

Birth Weight, Placental Weight and Apgar Score

The mean birth weight of all the live births in this series was 2952gm with a mean placental weight of 548.6gm. In term deliveries, there was no significant difference between the mean birth weight and placental weight in babies born to mothers treated with carbimazole and with the addition of propranolol (Table II and III).

Fetal Mortality and Morbidity

a) Perinatal Mortality

There were 2 perinatal deaths in this study. One premature baby was a fresh still birth following a breech extraction for cord prolapse. There was a neonatal death of a premature baby at 31 weeks with multiple congenital abnormalities. The mother had been on treatment prior to conception but as she declined post mortem, it was not possible to assess the true nature of the deformities. Neither was it possible to attribute this to teratogenicity due to the carbimazole. The average perinatal loss for all patients in this hospital during the years of study was 19.01 per 1000 births.

b) Neonatal Goitre and Thyroid Status

No neonatal goitre was observed in this series. All babies were assessed clinically at birth and in the post natal wards 24 hours later. Thyroid Function Test was done only in 7 cases suspected to have thyroid dysfunction. This was abnormal in only one baby delivered prematurely at 35 weeks gestation. The mother, who was unbooked, was euthyroid clinically and biochemically on admission and was on maintenance dose of 10 mg b.d. of carbimazole for the past 1 year. Her labour progressed satisfactorily and she delivered a female baby weighing 1680gm, Apgar 9/10 by spotaneous vertex delivery. The baby was assessed by the Paediatrician to be 35 weeks (appropriate for gestational age) and had no goitre or features of hypothyroidism. However, a diagnosis of Patent Ductus Arteriosus was confirmed later by Echo-cardiography. This was attributed to her fluid therapy and prematurity. Her Thyroid Function Test (TFT) was indicative of hypothyroidism. The baby developed neonatal jaundice which improved with phototherapy. A repeat TFT 1 week later showed results within normal limits. Follow-up of the baby at the Paediatric Clinic showed normal developmental milestones. No baby showed clinical features of cretinism in this study.

Table II
COMPARISON OF MEAN BIRTH WEIGHT IN 23 TERM DELIVERIES IN MOTHERS TREATED WITH CARBIMAZOLE WITH OR WITHOUT PROPRANOLOL

Drug used	No. of term deliveries	Mean birth wt. (± SD) (Grams)
Carbimazole	14	3146 (± 288)
Carbimazole + Propranolol	9	3074 (± 279)

P = >0.005

c) Fetal abnormalities

Congenital abnormalities were seen in 3 babies. One was born pre-term at 31 weeks with multiple congenital abnormalities which resulted in Neonatal Death 1 week later. The other congenital abnormalities were:

i) Patent Ductus Arteriosus
ii) Left Choanal Atresia

Table III

COMPARISON OF MEAN PLACENTAL WEIGHT OF 23 TERM DELIVERIES IN MOTHERS TREATED WITH CARBIMAZOLE WITH OR WITHOUT PROPRANOLOL

Drug used	No. of term deliveries	Mean placental wt. (± SD) (grams)
Carbimazole	14	626 (± 46)
Carbimazole + Propranolol	9	580 (± 43)

P = >0.05

DISCUSSION

In this retrospective study of 28 thyrotoxic pregnant mothers in a six-year period, there was 1 fresh stillbirth and 1 neonatal death. This is comparable with results in other series (2,13,14); neither death was attributable to the maternal thyrotoxicosis.

Management of hyperthyroidism during pregnancy aims at optimal control of the maternal condition, but therapeutic decisions should take the fetus into account, allowing for normal metabolism and growth. While small for dates babies have been reported to be associated with poor control in pregnancy (12), none of the babies in this series fell below the 10th percentile on the weight chart (15) when corrected for gestational age. The mean birth weight of all Malaysian babies at term is 3,159gm (16).

The use of propranolol did not appear to have any deleterious effect as far as birth weight, Apgar scores and placental weights are concerned. However, it must be noted that this drug when used, was given only for less than 8 weeks and small doses were used. Based on this evidence it would appear that propranolol is not contraindicated to control acute symptoms as long as careful monitoring is carried out.

There was no goitre seen in the babies of this series; however, an incidence of 5.1% has been reported by others (14). To date, there has been no explanation why goitre occurs in some babies and not in others. There is no direct correlation between increasing dosage of antithyroid drugs and the presence of fetal goitre (17).

Three of the 28 babies (10.7%) had congenital abnormalities. One had fatal multiple congenital abnormalities while the other 2 were of minor nature. None could be directly attributable to the usage of carbimazole. This rate is similar to the congenital abnormality rate seen in other series i.e. 9.5% (2). There were no scalp defects (aplasia cutis) as reported in babies born to mothers treated with methimazole (18).

In this study 9 patients received L-thyroxine supplementation. No difference in obstetric outcome was noted in these patients when compared with those who were managed solely with carbimazole. Carbimazole was the mainstay of treatment as this was easily available although propylthiouracil has more theoretical advantages. Although the consensus opinion is that L-thyroxine supplementation is not indicated (18,19), proponents of this regime (2) feel that control of symptoms is smoother. It is, therefore, difficult to determine which form of medical therapy is optimal as there is yet to be a prospective randomized trial comparing antithyroid drugs alone versus antithyroid drugs with thyroid hormone supplementation.

While the results of such a study are awaited, the choice of treatment still depends on the experience of the attendant physician, expert clinical judgement in conjunction with effective antenatal, intra-partum and postnatal care.

REFERENCES

1. Goluboff LG, Hamburger JI. Hyperthyroidism associated with pregnancy. Obstet Gynecol 1974; 44:107-55.
2. Burrow GW. Thyroid diseases In Burrow and Ferris ed. Medical Complications during pregnancy. Philadelphia: WB Saunders Co, 1988; 238-42.
3. Gardiner-Hill H. Pregnancy complicating simple goitre and Grave's disease. Lancet 1929; i:120-4.
4. Becker WF, Sudduth PG. Hyperthyroidism and pregnancy. Ann Surg 1959; 145:867-74.
5. Refetoff S, Ochi O, Selenkow HA, Rosenfield RL. Neonatal hypothyroidism and goitre in one infant of each of two sets of twins due to maternal therapy with antithyroid drugs, J Pediatr 1974; 85:240-4.
6. Gladstone GR, Hordof A, Gersony WM. Propranolol administration during pregnancy: Effects on the fetus. J Pediatr 1975; 86:962-4.
7. Buchanan N. Drugs in pregnancy and Lactation. J Paeds Obstet Gynaecol 1987; 13:16.
8. Rubin PC. Beta-blockers in pregnancy. N Engl J Med 1983; 18:73.
9. Marchant B, Brownlie BEW, McKay Hart D, Horton PW, Alexander WD. The Placental transfer of Propylthiouracil, Methimazole and Carbimazole. J Clin Endocrinol Metab 1977; 45:1187-93.
10. Ramsay I, Kaur S, Krassas G. Thyrotoxicosis in pregnancy: Results of treatment by antithyroid drugs in combination with T4. Clin Endocrinol 1983; 18:73-85.
11. British Births 1970 Vol 1: The first week of life. London: Heinnemann, 1975:51.
12. Niswander KR, Gordon M, Berendes AW. The women and their pregnancies. Philadelphia: WB Saunders, 1972:77.
13. Talbert LM, Thomas GC, Rankin P. Hyperthyroidism during pregnancy. Obstet Gynecol 1970; 36:779-85.
14. Sugrue D, Drury MI. Hyperthyroidism complicating pregnancy: Results of treatment by antithyroid drugs in 77 pregnancies. Br J Obstet Gynaecol 1980; 87:970-5.
15. Lubchenco LO, Hansman C, Boyd E. J Pediatr 1963; 32:793.
16. Yusof K, Sinnathuray TA. Fetal growth patterns in normal Malaysian pregnancies. Aust NZ J Obstet Gynaecol 1976; 16:213-6.
17. Burrow GN. Neonatal goitre after maternal propylthiouracil therapy. J Clinc Endocrinol Metab 1965; 25:403-8.
18. Mutjaba Q, and Burrow GN. Treatment of hyperthyroidism in pregnancy with propylthiouracil and methimazole. Obstet Gynecol 1975: 46:282-6.
19. Hamburger JI. Management of the pregnant hyperthyroid; the argument against combined antithyroid-thyroid therapy. Obstet Gynecol 1972; 40:114-7.