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Graves' Disease During Pregnancy – Results of Antithyroid Drug Therapy

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ABSTRACT

Aim of Study: To assess the maternal and fetal outcome of pregnancies in thyrotoxic women.

Method: Thyrotoxic women who conceived while on treatment or who conceived within two years after stopping treatment, were recruited into the study. The antithyroid drugs (PTU and methimazole) dosage were adjusted to keep T3 and T4 within the upper normal range for these women. Cord blood and baby's blood (between days 4 and 10) were assayed for T3, T4 and TSH.

Results: Thirteen women (16 pregnancies) required antithyroid drugs during pregnancy. The drug dosage remained the same during pregnancy in 8 women while it was increased in 5 women and reduced in 3 women. One woman who was in remission at the time of conception remained euthyroid throughout her pregnancy. There were 14 spontaneous vaginal deliveries and 3 Caesarean sections. One baby had a small VSD while no other congenital malformations or perinatal death occurred.

Conclusion: Drug therapy can adequately control thyrotoxicosis during pregnancy and improve maternal and fetal outcome.

Keywords: hyperthyroidism, pregnancy complication, drug therapy, propyl thiouracil, carbimazole, neonatal screening

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INTRODUCTION

Thyrotoxicosis is rare (0.2%) among pregnant women[1] but the combination is of importance because it can be a major hazard for the pregnant woman and her developing fetus. It may lead to preterm labour, thyrotoxic crisis and fetal death. Without specific antithyroid treatment, fetal loss may be as high as 48%[2].

Thyrotoxicosis can be adequately controlled with antithyroid drug, therefore the disease poses no significant threat to the mother. However, inadequate or excessive medication can lead to fetal complications. Here, we report our experience with antithyroid drug therapy for Graves' disease during pregnancy.

PATIENTS AND METHODS

Women with Graves' disease who conceived while undergoing treatment at the Endocrine Clinic of our hospital, were also followed-up in the antenatal clinic for any pregnancy-related complications and fetal growth. Women who could afford propyl thiouracil (PTU) were advised to change over to PTU. (PTU is not easily available and is more expensive whereas neomercazole (carbimazole) is freely available available). Those who could not afford PTU continued on neomercazole. The dosage of antithyroid drug was adjusted in such a way as to maintain serum T3, T4 levels in euthyroid or mildly thyrotoxic range. Drugs were stopped 1 week before the expected date of delivery. Further treatment was decided depending on the thyroid status postpartum. All deliveries were conducted in the hospital. Serum T3, T4 and TSH levels were assayed in cord blood. In cases where cord blood was tested again between days 4 and 7, appropriate treatment was advised. Mothers were advised to breastfeed their infants and both were followed-up for 6 months. T3, T4 and TSH were estimated by RIA using commercially available reagents from BARC, Bombay.

RESULTS

A total of 16 pregnancies in 13 women, aged 21 to 35 years were studied. Eight of these women were less than 25 years old. Four were between 25 – 30 years old and 1 was more than 30 years old. Details of their age, parity, previous pregnancies, duration of illness and previous treatment are given in Table I. One woman had a history of abortions and one had a stillborn child. All of them had a history suggestive of thyrotoxicosis and two of them had received antithyroid medication in suboptimal doses.

The duration of thyrotoxicosis ranged from 2 to 48 (21+11.9) months. They were on variable doses of neomercazole or PTU. Details are given in Table II.

Ten women had diffuse thyromegaly (grade 1 to 2), and 8 had exophthalmos (grade 2 to 4, no specs grading). One patient had a cerebellar haemangioma operated 2 years prior to this pregnancy without residual neurological deficit. Blood sugar levels were normal in all these patients.

Six women changed to PTU and 7 continued on neomercazole during pregnancy. Seven patients were euthyroid at the time of conception. Four women became euthyroid during the first trimester. Patient number 12 required an unusually large dose (60 mg daily) of neomercazole, reaching euthyroid status only in her third trimester.

Table I – Details of patients' age, obstetric history and past medical treatment

Patient No.	ID	Age	Obstetric history Parity	Deliveries	Caesarean	Thyrotoxicosis Duration (months)	Treatment
1a	AK	24	PRIMI	0	N	2	NMZ
1b	AK	26	G2	1	N	24	NMZ, PTU
2a	SB*	24	G2	0	N	18	NMZ
2b	SB	25	G3	1	N	30	NMZ
3	RJ	29	G3	2	N	18	NMZ, PRL
4	NK	24	G2	1	Y	12	NMZ
5a	RS**	26	G2	1	N	5	NMZ, PRL
5b	RS	27	G3	1	N	24	NMZ, PTU
6	SG	25	PRIMI	0	N	12	NMZ
7	KI#	21	G4	1	Y	48	NMZ
8	KM@	26	G5	4	N	18	NMZ
9	MK	25	PRIMI	0	N	12	NMZ
10	RA	26	PRIMI	0	N	12	PTU
11	RG	35	G3	2	N	4	NMZ
12	AN	22	G2	1	N	12	NMZ
13	PU	27	G2	1	N	24	NMZ

* Stillbirth prior to first delivery, G : gravida
PRIMI : primigravida; NMZ : carbimazole,
PRL : propranolol; N : No, Y : Yes
PT : Propyl thiouracil
@ Patient was operated for cerebellar haemangioma
** One abortion prior to first delivery
# Two abortions prior to first delivery

Table II – Details of drug therapy during pregnancy

No.	Patient	Drug and dose First trimester	Second trimester	Third trimester	Post-partum Remission
1a	AK	PTU 150	PTU 200	PTU 400	No
1b	AK	PTU 200	PTU 200	PTU 200	Yes
2a	SB	NMZ 20	NMZ 20	NMZ 20	No
2b	SB	NMZ 20	NMZ 20	NMZ 20	No
3	RJ	PTU 100	PTU 100	PTU 100	Yes
4	NK	NMZ 5	NMZ 5	NMZ 5	Yes
5a	RS	PTU 200	PTU 300	PTU 300	No
5b	RS	PTU 100	PTU 150	PTU 150	Yes
6	SG	PTU 200	PTU 100	-	Yes
7	KI	NMZ 10	NMZ 10	-	Yes
8	KM	NMZ 20	NMZ 30	NMZ 60	No
9	MK	NMZ 20	NMZ 20	NMZ 20	No
10	RA	PTU 300	PTU 200	PTU 100	Yes
11	RG	PTU 100	PTU 100	PTU 100	No
12	AN	NMZ 15	NMZ 15	NMZ 15	Yes
13	PU	NMZ 15	NMZ 10	NMZ 10	Yes

N : Not in remission, drug continued
Y : In remission, not on antithyroid drugs
- : No antithyroid drugs

Drug requirement decreased in 3 (18.8%) women as their pregnancy advanced. Five (31.2%) women required an increase in their drug dosage. Others (50%) required the same dose throughout their pregnancy. Three women had pregnancy-induced hypertension. Three women required Caesarean section (2 breech presentation and 1 cord around the neck). Eight were spontaneous vaginal deliveries and 5 had to be induced between 38 and 40 weeks of gestation.

None of the neonates had goitre or clinical evidence of thyroid dysfunction. One baby had a small VSD. There were 3 babies whose birth weight was less than the 10th percentile[3]. Thyroid hormone profile of the neonates and details of maternal drug requirement at the time of delivery are given in Table III. There were 2 neonates whose cord blood TSH was more than 10 mIU/mL. Both normalised by day 7. Their mothers were on relatively higher doses of drugs (400 mg of PTU, 60 mg of neomercazole) during the third trimester. There were no pregnancy losses or perinatal deaths in this study group though six women required drugs during the postpartum period.

DISCUSSION

Astwood was the first to report the successful treatment of hyperthyroidism in pregnant women with medical therapy alone. He treated 19 thyrotoxic women with a total of 22 pregnancies with PTU. There were 19 term and 3 pre-term deliveries. There was no fetal loss, goitre or hypothyroidism. He started his patients' treatment regimen with full therapeutic doses to attain euthyroid status and then continued their treatment with smaller doses (150 mg daily) during the later part of gestation.

Considering the difficulties in clinical evaluation of thyroid status in pregnant women, he also suggested an alternative method, ie. use of full doses of antithyroid drug with thyroid supplement. Larger doses of antithyroid drug would insure against thyrotoxicosis while thyroxin would prevent hypothyroidism.

Herbst and Selenkow as well as other workers[5-7] had treated thyrotoxicosis in pregnancy with combined thyroid-antithyroid therapy. They claimed that results of combined therapy were superior to the use of antithyroid drugs alone. However, some physicians argued against the use of combined therapy[8,9]. Opponents of combined therapy were of the opinion that this (combined therapy) would only serve to increase the fetal exposure to antithyroid drugs. They suggested proper reduction in the dosage of antithyroid drugs as the patient becomes euthyroid with free thyroxin index as the guideline.

Thionamides are the mainstay of drug therapy for Graves' disease during pregnancy. Transplacental passage of PTU is less than carbimazole. Aplasia cutis (in neonates) has been reported with the use of carbimazole though no teratogenicity has been reported with PTU. Therefore PTU is the preferred antithyroid drug in pregnancy. However, this is not

Table III – Details of neonates at birth

Patient No.	ID	Weight (kg)	Apgar score	Drug & dose **	T3 ng/mL	T4 ug/dL	TSH mIU/mL
1a	AK	2.78	9/10	PTU 400	152	9.6	8.9
1b	AK	3.2	9/10	PTU 200	105	10.6	5.2
2a	SB	2.53	9/10	NMZ 20	173	9.8	4.9
2b	SB	2.07	8/10	NMZ 20	160	11	4.6
3	RJ	2.56	9/10	PTU 100	60	7	2
4	NK	2.8	9/10	NMZ 5	92	7.6	20
5a@	RS	2.46	9/10	PTU 300	92	12.8	6.6
5b	RS	2.3	9/10	PTU 150	135	8.9	0.6
6	SG	2.36	9/10	*	140	12	8.6
7	KI	2	9/10	*	120	8	2.2
8	KM	2.87	9/10	NMZ 60	90	9.1	18.5
9	MK	2.65	9/10	NMZ 20	100	12.3	6.4
10	RA	2.86	9/10	PTU 100	160	10.2	14
11	RG	2.53	9/10	PTU 100	-	1.8>	1.2
12	AN	2.9	9/10	NMZ 15	-	5	35
13	PU	2.86	9/10	NMZ 10	95	7	1.4

@ Child had VSD, ** during third trimester, > FT4

Normal range
T3 : 30 – 70 ng/mL
T4 : 8 – 13 ug/dL
TSH : 3 – 12 mIU/dL

* no antithyroid drugs

based on statistically established clinical data[10]. Propranolol can cause neonatal hypoglycaemia, fetal bradycardia and IUGR. It is used in severe cases as a temporary measure[10]. Table IV summarises maternal and fetal outcome of pregnancies in thyrotoxic women published since 1980.

In the present study, 16 pregnancies in 3 women with Graves' disease were studied. These women were on antithyroid drugs. Seven pregnancies occurred after euthyroid status was achieved and 6 women (8 pregnancies) changed over to PTU and the others continued on neomercazole. Drug dose was adjusted in such a way as to maintain T3, T4 levels in euthyroid or mildly thyrotoxic range. Drug requirement ranged from 100 mg to 400 mg of PTU or 5 mg of PTU or 5 mg to 60 mg of NM daily. Drug requirement decreased in 3(18.8%) women as the pregnancy advanced. It remained the same in 8 (50%) women and increased in 5 (31.2%) women.

Three women (21.4%) had pregnancy-induced hypertension. There were 8 spontaneous vaginal deliveries and five were induced between 38 and 40 weeks of gestation. Three were delivered by Caesarean section (for reasons unrelated to thyroid status).

There were no abortions, stillbirths or preterm labour. Birth weight of the infants ranged from 2 kg to 3.2 kg (mean 2.6 kg). There were three babies who weighed less than 2.5 kg. There were no congenital

Table IV – Summary of outcome of pregnancies in thyrotoxic women published (since 1980)

SL No	Author(s)	Year	Publication	W/P	Drugs			Pregnancy loss		Details of Neonates				Monitering
					CMZ (mgs)	PTU (mgs)	MMI (mgs)	Foetal	Perinatal	C.A.	N.T.	Goitre	Birth weight	
1.	Sugrue	1980	Br J Ob Gy	77	5.10	-		15.2%	5.1%	1	NR	5.1%	85.1% 25th Centile	NR
2.	B A Lamberg	1981	Acta Endo	11	35	200	-	NR	NR	NR	Nil	Nil TSH in 1	2 < 3 SD	FT 41
3.	L E Davis	1981	Am J Ob Gy	60	-	300 to 800	15	NR	NR	NR	1	2	4 small for age	NR
4.	I Ramsay	1983	Clin Endo	19/20	20 to 60 + T4	-	-	NR	NR	2	1	1	No sig. diff.	NR
5.	Gopee Singh	1983	W Ind Med J	11/17	11 pts	-	-	3	-	-	1	-	-	T3, T4
6.	Momotani	1984	NEJM	70	-	450	20	3	Nil	NR	NR	NR	NR	T3, T4
7.	Collen Stice (retrospective)	1984	Surg Ob Gy	25							Nil	Nil	NR	
8.	B H Lim	1989	Singapore Med J	28	Yes	-	-	NR	NR	-	-	No	Mean 2952 gms	NR
9.	Mortimer	1990	Clin Endo	44/46	5 to 45	50 to 400	-	NR	NR	NR	8%	NR	NR	T3, FT41 TB11, TSH
10.	Mitsuda	1992	Ob Gy	172/230	60 pts	31pts	20 pts						-	

CMZ : Carbimazole, PTU : Propyl Thiouracil, MMI : Methimazole, W : Women, P : Pregnancies, CA : Congenital anomalies, N.T. : Neonatal Thyotoxicosis, NR : Not reported

malformations except for a small VSD. Two babies had cord TSH more than 10 mIU/mL and 35 mIU/mL). Both normalised by day 7. No goitre, hypothyroidism or neonatal thyrotoxicosis was noted. Our results compare favourably with those of Astwood[4] and Ramsay[8].

A previous study from this Institute showed prevalence of thyrotoxicosis among pregnant women to be 0.26%. Maternal and fetal outcome was significantly poorer in pregnancies complicated by thyrotoxicosis. Diagnosis of thyrotoxicosis in some of those women was made during different stages of pregnancy. Several of them were still thyrotoxic in the third trimester because of poor compliance and/or late diagnosis.

In the present study, the diagnosis of Graves' disease was made prior to pregnancy and all were on treatment and regular follow-up at the time of conception. Three of these women had previous unsuccessful pregnancies possibly due to undiagnosed/untreated thyrotoxicosis.

We conclude that medical treatment with thionamides alone is a safe and effective therapy for thyrotoxicosis during pregnancy. Drug dose needs to be adjusted with frequent T3, T4 measurements. Pre-pregnancy counselling is important. Thyrotoxic women who wish to conceive should be advised to plan their pregnancy after treatment or at least after attaining euthyroid status.

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Corrigendum

The author of the following article, *Clinics in Diagnostic Imaging (33)* (Singapore Med J 1999; 40 (1): 53-56), wishes to apologise for an oversight in the labelling of one of the figures. The correct figure is printed herewith with the legend.

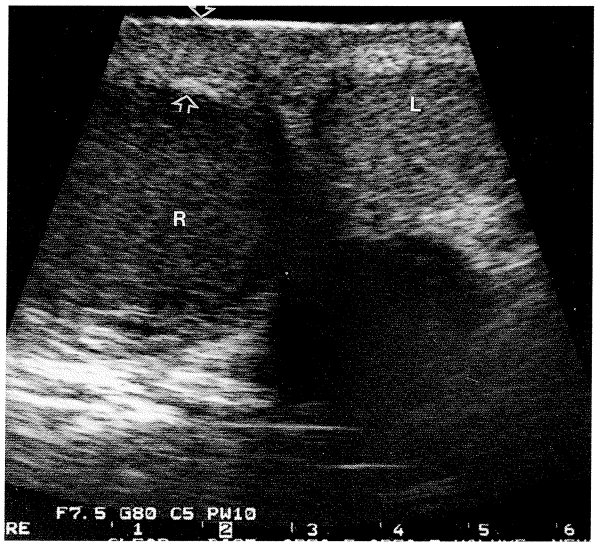

Fig 4: Right epididymo-orchitis. Transverse US scans of both testes show diffuse homogeneously-decreased echogenicity of the enlarged right testis [R] with thickened right scrotal skin (open arrowhead). Left testis [L] is normal.