

# A retrospective analysis of thyroid disease in pregnancy at Chris Hani Baragwanath Academic Hospital, Soweto, South Africa

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**Background.** Thyroid diseases in pregnancy are associated with adverse outcomes for both mother and fetus. No studies have been reported examining the spectrum and nature of such disorders in the black population of South Africa.

**Objective.** To examine thyroid disorders in pregnancy at Chris Hani Baragwanath Academic Hospital in Johannesburg, Soweto, by assessing the causes, management and outcomes.

**Methods.** A retrospective review of thyroid disorders was undertaken in 88 patients attending the Antenatal Endocrine Clinic over a 4-year period. All underwent initial and follow-up clinical and biochemical assessments. Maternal delivery records and thyroid-function tests of the neonates  $\geq 48$  hours after delivery were reviewed.

**Results.** A total of 58 pregnant women (66%) were hyperthyroid, 23 (26%) hypothyroid and 7 (8%) had euthyroid colloid goitres. Forty-eight (83%) hyperthyroid patients had Graves' disease, while 9 (16%) had gestational hyperthyroidism. Regarding the hypothyroid patients, more than half followed I131 ablation for Graves' disease. Overall, 87% of the hyperthyroid and 83% of the hypothyroid patients were euthyroid prior to delivery. One fatal maternal outcome, the result of uterine rupture, and six intra-partum fetal losses occurred. Amongst neonates, there was one case of a tracheo-oesophageal fistula and one of neonatal thyrotoxicosis.

**Conclusion.** This is the first report in sub-Saharan Africa detailing thyroid diseases in pregnancy. Our findings add valuable epidemiological information to the paucity of data that has previously existed for thyroid disease in pregnancy in sub-Saharan Africa.

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Over the past two decades, there have been several studies examining thyroid disorders in pregnancy, but none in South Africa.<sup>[1,2]</sup> The prevalence of hyperthyroidism is 0.1 - 0.4% of all pregnancies in developed nations, with Graves' disease (GD) accounting for the majority of cases (85%). Hypothyroidism is estimated to occur in 2.3 - 3.5% of pregnancies, of which overt hypothyroidism accounts for 0.3 - 0.5%, and subclinical hypothyroidism for 2 - 3% in iodine-sufficient areas.<sup>[1,3]</sup> Data from a 2001 study demonstrated that more than one-third of South Africans are still iodine deficient, with endemic goiter being the most prevalent thyroid disorder.<sup>[4]</sup>

The importance of thyroid disease in pregnancy is determined by the potential adverse outcomes of untreated disease for both mother and fetus.<sup>[5,6]</sup> While the diagnosis, evaluation and treatment are similar to those in the non-pregnant state, pregnancy poses its own unique challenges.

Our study was carried out at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, which is the largest hospital in Africa and serves a largely black population. We describe the underlying causes, management, control and outcomes of thyroid diseases in pregnancy.

## Methods

### Study population

We reviewed 88 patients with a thyroid disorder who attended our Antenatal Endocrine Clinic from January 2004 to April 2008.

These patients included those with a pre-existing thyroid disorder and those in whom a diagnosis was made for the first time during pregnancy. A multidisciplinary team consisting of an obstetrician, endocrinologist and nurse educator managed the patients.

### Data collection

At initial assessment, maternal characteristics, such as age, parity, duration of gestation and the cause of the thyroid disorder, were documented. Baseline investigations examined thyroid-stimulating hormone (TSH), free thyroxine (FT4) concentrations, antithyroperoxidase antibodies (TPO-Ab) and antithyroglobulin antibodies (TG-Ab).

Patients were considered to have GD if they had a previous history of known GD, or were biochemically hyperthyroid with evidence of ophthalmopathy, dermopathy or thyroid-antibody positivity. FT4 and TSH were monitored monthly, and treatment was adjusted as necessary.

Delivery records of mothers were reviewed. Neonatal thyroid-function testing was performed at or after 48 hours of age. Adverse fetal outcomes noted were those of low birth weight (LBW), premature delivery, congenital abnormalities and neonatal deaths.

Maternal outcomes included caesarean section rates, maternal complications, spontaneous miscarriage and intrauterine fetal deaths (IUFDs).

## Assays

FT4 and TSH concentrations were measured by Cobas electrochemiluminescence-immunoassay (Roche Diagnostics GmbH, Germany). The adult reference ranges were TSH 0.35 - 4.5 mIU/L and FT4 11 - 21 pmol/L. The trimester-specific TSH reference ranges were first trimester 0.1 - 2.5 mIU/L, second trimester 0.2 - 3.0 mIU/L and third trimester 0.3 - 3.0 mIU/L. For FT4, the non-pregnant reference range (12.0 - 22.0 pmol/L) was utilised, since our laboratory has not established trimester-specific reference ranges. The limit of detection for TSH was 0.005 mIU/L, and 0.3 pmol/L for FT4. Inter-assay coefficients of variation were 3.5 - 5.9% for TSH, and 4.1 - 4.3% for FT4.

TPO-Ab and TG-Ab levels were measured using a passive haemagglutination assay (Remel, UK).

When more than one TSH and FT4 measurement was made in a particular trimester, the median (interquartile range) was calculated and utilised. Patients were considered to be euthyroid if their TSH was within the trimester-specific reference range and the FT4 was normal. If both were abnormal, they were classified as either hypothyroid or hyperthyroid. The reference ranges for neonates aged 2 - 5 days were TSH 0.7 - 15.2 mIU/L, and FT4 11 - 32 pmol/L.

## Definitions

The first trimester of pregnancy was considered to last until 12 completed weeks, the second from week 13 to 27, and the third from week 28.

A fetus that had died after the 26th week of gestation was considered to be an IUFD.

A spontaneous miscarriage was defined as spontaneous loss of the conceptus prior to 26 weeks' pregnancy, or one in which the mass of the fetus was <600 g. Premature delivery was considered to be a delivery occurring prior to the 37th week of gestation. LBW was defined as a fetal weight <2 500 g. A low Apgar score was defined as a mean fetal score  $\leq 7$  points at 5 minutes. Thyroid-antibody status was considered positive if either the TPO-Ab or TG-Ab test was positive.

## Statistical analysis

Values are presented as means (standard deviation (SD)) for normally distributed data, and otherwise as medians and interquartile ranges (IQRs), with categorical variables expressed as percentages. Differences between groups were assessed using the  $\chi^2$  test for the categorical variables and with the Wilcoxon-Mann-Whitney test and *t*-test for quantitative variables. Results were statistically significant for all *p*-values <0.05.

## Results

The prevalence rate of thyroid disease was 0.08%, among ~102 000 women attending the general antenatal clinic at CHBAH over the same period. The prevalence rates of GD and overt hypothyroidism were 0.05% and 0.02%, respectively.

## Maternal demographics and thyroid status

The mean (SD) age was 29 (5.8) years, and mean (SD) duration of gestation 19.8 (8.5) weeks. A total of 58 (66%) thyroid patients were hyperthyroid (either pre-existing or newly diagnosed during the pregnancy), 23 (26%) were hypothyroid and 7 (8%) were euthyroid. Sixty-eight (77%) patients had a known pre-existing thyroid disease, and in 20 (23%) it was detected for the first time during pregnancy.

Thyroid-antibody status, including TPO-Ab and TG-Ab, was available for only 42 (48%) of the patients. Of these, 13 (31%) patients tested positive and 29 (69%) tested negative (Table 1). Thyroid biochemistry profiles for the various groups, at presentation and delivery, are shown in Table 2.

Seven mothers were documented with cardiac failure at presentation, all in patients with GD. Four of the 7 were in the newly diagnosed group, and 3 in the pre-existing group.

## Patients with hyperthyroidism

Of the 58 patients with hyperthyroidism, 48 (83%) had GD, and 9 (16%) had gestational thyrotoxicosis (GTT). One patient had a molar pregnancy.

**Table 1. Maternal demographics**

	All patients (N= 88)	Hyperthyroid (n=58)	Hypothyroid (n=23)	Euthyroid colloid goitre (n=7)
Age (years), mean (SD)	29.0 (5.8)	27.9 (5.8)	30.9 (5.6)	31.4 (5.4)
Gestational age at presentation (weeks), mean (SD)	19.8 (8.5)	18.8 (8.6)	21.0 (8.2)	24.1 (7.3)
Pre-existing thyroid disorder, n (%)	68 (77.3)	41 (70.7)	23 (100)	4 (57.1)
Thyroid-antibody status positive, %	31.0 (13/42*)	31.3 (10/32*)	50 (3/6*)	0 (0/4*)

\*Results for thyroid antibodies (TPO-Ab and TG-Ab) were available for 42 of the 88 patients: 32 in the hyperthyroid group, 6 in the hypothyroid group and 4 in the euthyroid group. SD = standard deviation.

**Table 2. Thyroid-function tests of each group at presentation and delivery, median (IQR)\***

	At presentation, n=88				At delivery, n=70			
	n	TSH (mIU/L)	FT4 (pmol/L)	Euthyroid, n (%)	n	TSH (mIU/L)	FT4 (pmol/L)	Euthyroid n/N (%)
Hyperthyroid	58	0.02 (0.01 - 0.45)	23.8 (12.9 - 44.1)	21 (36)	46	0.96 (0.01 - 2.01)	13.1 (11.9 - 14.4)	39/45 <sup>†</sup> (87)
Hypothyroid	23	7.36 (1.56 - 16.9)	11.0 (7.0 - 14.3)	6 (30)	18	1.85 (0.57 - 3.35)	14.1 (12.3 - 15.9)	15/18 <sup>†</sup> (83)
Colloid goitre	7	1.02 (0.06 - 1.32)	13.0 (10.9 - 15.1)	7 (100)	6	0.89 (0.44 - 1.25)	13.0 (9.4 - 15.2)	6/6 <sup>†</sup> (100)

IQR = interquartile range; TSH = thyroid-stimulating hormone; FT4 = free thyroxine.

\*Unless otherwise indicated.

<sup>†</sup>Thyroid function results available in 69 patients: 45 in the hyperthyroid group, 18 in the hypothyroid group and 6 in the euthyroid group.

## Graves' disease

The mean (SD) age of the hyperthyroid GD patients was 28 (5.7) years. The mean (SD) time of presentation was at 19 (8.8) weeks of pregnancy. Antibody status was known in 28 of 48 GD patients: 10 (36%) were positive and 18 (64%) negative. A total of 38 (79%) of the 48 patients with GD had established pre-existing disease, while the remaining 10 (21%) were diagnosed with Graves' hyperthyroidism during pregnancy.

Of the pre-existing GD patients ( $n=38$ ), 58% were biochemically euthyroid at first presentation, with 42% being thyrotoxic.

Thyroid-function tests were available for 40 patients at delivery. These showed that 32 (80%) were euthyroid at delivery. Fifty percent of pre-existing GD patients who were thyrotoxic at first presentation were rendered euthyroid at delivery with the appropriate use of carbimazole only (Table 3).

## Non-GD hyperthyroid

The mean (SD) age of the 10 non-GD hyperthyroid patients, at presentation, was 29 (6.0) years, and their mean (SD) gestational age at first presentation was 18 (8.1) weeks. This group consisted of 3 hyperemesis gravidarum patients, 1 patient with a molar pregnancy and 4 patients in whom the cause was unknown. The remaining 2 patients had been lost to follow-up at an early stage. Thyroid antibodies were negative in the 4 patients for whom a result was available.

## Patients with hypothyroidism

The mean (SD) age at presentation of the 23 hypothyroid patients was 31 (5.6) years, and their mean (SD) gestational age was 21 (8.2) weeks. The majority was made up of 12 patients (52%) who were former GD patients who had been ablated with radioiodine, 6 (26%) who were post-thyroidectomy and 4 (17%) with confirmed Hashimoto's disease. One had congenital hypothyroidism (Table 2). At first presentation to our clinic, the majority of patients (57%) had overt hypothyroidism, with 22% having subclinical disease, i.e. normal FT4 with a raised TSH above the trimester-specific reference range. A total of 18 of the 23 patients had thyroid-function results available at delivery, of whom 15 (83%) had normal thyroid-hormone levels as a result of their thyroxine replacement therapy (Table 3).

## Patients with a euthyroid colloid goitre

The seven euthyroid patients were identified owing to the presence of a goitre. All were euthyroid at presentation and throughout their pregnancies.

## Maternal outcomes

There was one maternal death in a patient with a euthyroid goitre, secondary to uterine rupture, following induction of labour at 38 weeks.

The two spontaneous miscarriages were in patients with cardiac failure, who miscarried a few weeks thereafter. Most deliveries ( $n=49$ ; 88%) occurred at term, while seven (12%) were premature deliveries.

## Fetal outcomes

A total of 80% of the neonates had normal birthweights (mean (SD) 2 895 (495) g). The remaining 20% had LBW (<2 500g), of which 4 were premature deliveries. Nine of the mothers with LBW babies had GD, of whom 7 were euthyroid and 2 were hyperthyroid at delivery. The remaining 2 were patients from the hypothyroid group, and were still mildly hypothyroid at delivery.

There were 6 fetal losses, 4 being IUFDs and 2 spontaneous miscarriages. Two of the IUFDs presented for the first time late in pregnancy, one as hyperthyroid and the other hypothyroid.

One baby was macrosomic (4 030 g), born to a mother with a euthyroid colloid goitre and no other comorbidity. Apgar scores were similar in the hyper- and hypothyroid groups (medians of 9 and 10 at 1 and 5 minutes, respectively, in both groups).

Thyroid-function tests in 35 neonates were normal, except for one case of neonatal thyrotoxicosis, which was reconfirmed at 3 weeks of age (TSH  $\leq 0.01$  mIU/L and FT4  $>100$  pmol/L), who was born to a mother with newly diagnosed GD in pregnancy.

Two neonates were born with congenital anomalies, one with polydactyly, and one with a trachea-oesophageal fistula (TOF). The infant with the TOF was born to a mother who presented during the first trimester. She had pre-existing GD and was thyrotoxic, and treated with a high dose of carbimazole.

## Discussion

Thyroid disease in pregnancy remains an area of public health concern, and in recent years clinical guidelines have addressed this issue.<sup>[7,8]</sup>

There are very few epidemiological studies assessing the prevalence of thyroid disease in pregnancy, and this is the first comprehensive report from Africa.

Within our hyperthyroid group, not surprisingly, GD was by far the most common disorder encountered. The frequency of 0.05% of all pregnancies managed at our institution was lower than the 0.2 - 0.4% reported by others.<sup>[9]</sup> This may possibly be attributable to the lack of universal screening in our setting. In addition, some patients may have been misclassified as having GTT, rather than

**Table 3. Characteristics of patients with Graves' disease\***

	Age (years)	GA (weeks)	n	At presentation		At delivery		
				TSH (mIU/L)	FT4 (pmol/L)	n	TSH (mIU/L)	FT4 (pmol/L)
Pre-existing GD	28.3 (5.3)	17.9 (8.8)	38	0.03 (0.01 - 1.1)	15.4 (12.1 - 41.0)	34	0.96 (0.03 - 1.86)	13.1 (11.9 - 14.4)
Newly diagnosed GD	25.6 (6.9)	22.6 (7.9)	10	0.01 (0.01 - 0.01)	69.8 (60.8 - 100)	6	0.01 (0.01 - 2.01)	15.3 (9.8 - 60.8)
p-value	0.19 <sup>†</sup>	0.13 <sup>†</sup>		0.03 <sup>‡</sup>	<0.00 <sup>‡</sup>		0.32 <sup>‡</sup>	0.41 <sup>‡</sup>

GA = gestational age.

\*All continuous variables are expressed as means (SD); TSH and FT4 levels are expressed as medians and interquartile ranges.

<sup>†</sup>p-values for age and GA calculated using a t-test.

<sup>‡</sup>p-values for TSH and FT4 levels calculated using the Wilcoxon-Mann-Whitney test.

GD, owing to the unavailability of (Thyroid Stimulating Hormone Receptor Antibody) TRAb testing.

The prevalence of GTT in our cohort was only 0.008%, which was considerably lower than the 2 - 11% reported in the literature.<sup>[10]</sup> This is most likely the result of the fact that the mean gestational age at first presentation was 20 weeks, well beyond the time at which most GTT patients present.

The frequency of thyroid-antibody positivity of 36% in our patients with GD is considerably lower than that in data published for non-pregnant individuals.<sup>[11,12]</sup> Few studies have evaluated thyroid-antibody status in healthy African patients.<sup>[13-18]</sup> It is, however, known that thyroid-antibody levels decline progressively during pregnancy in healthy women without a thyroid disorder.<sup>[19]</sup> This is the result of the immune-privileged state. The majority of our GD patients first presented relatively late, well into the second trimester.

Hashimoto's thyroiditis was relatively uncommon, being rare in black South Africans.<sup>[11]</sup> Furthermore, it is not common in women of childbearing age.

Overall, hyperthyroidism was successfully managed, 87% having been rendered euthyroid by the time of delivery.

Six adverse obstetric outcomes occurred – four IUFDs and two spontaneous abortions. While most neonates delivered were of normal weight, as many as 20% were born with a LBW. Four were born to mothers who were either hyper- or hypothyroid at delivery.

Of the two neonates with congenital anomalies, one had polydactyly, a not uncommon anomaly found in the black South African population. Another had a TOF, an abnormality which may occur as part of a postulated 'methimazole embryopathy'.<sup>[20]</sup>

The limitations of this study include its retrospective nature, the small number of patients, the fact that some patients were lost to follow-up and the unavailability of TRAb measurements.

## Conclusion

To date, this is the first report on thyroid diseases in pregnancy in Africa. Despite limitations, our findings add valuable epidemiological information to the paucity of data that has previously existed for thyroid disease in pregnancy in sub-Saharan Africa. As the way forward, a prospective study is planned wherein high-risk individuals will be screened with documentation of maternal and fetal outcomes.

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