

**A Retrospective Analysis of Thyroid Disease in Pregnancy at Chris Hani
Baragwanath Academic Hospital, Soweto, South Africa**

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**A research report submitted to the University of the Witwatersrand,
Johannesburg in fulfillment for the requirements of the degree of Master
of Medicine 2015.**

DECLARATION

I, Veronique Nicolaou, declare that this research report is my own work, which is being submitted for the degree Master of Medicine (in the submissable format with my protocol and extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university

.....

.....day of2015

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PRESENTATIONS ARISING FROM THIS PROJECT

1. Poster presentation

A Retrospective Analysis of Thyroid Disease in Pregnancy at Chris Hani

Baragwanath Academic Hospital, Soweto, South Africa.

Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

Congress, Bloemfontein, 16-19th April 2015.

2. Oral presentation

A Retrospective Analysis of Thyroid Disease in Pregnancy at Chris Hani

Baragwanath Academic Hospital, Soweto, South Africa.

Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

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3. Submission for publication to the European Thyroid Journal

A Retrospective Analysis of Thyroid Disease in Pregnancy at Chris Hani

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ABSTRACT

Background

Hyperthyroidism occurs in 0.1-0.4% of pregnancies, Graves' disease accounting for 85% of cases. Hypothyroidism occurs in 2.3-3.5% of pregnancies, of which overt hypothyroidism accounts for 0.3-0.5% and subclinical hypothyroidism for 2-3%. Thyroid disease in pregnancy is known to be associated with adverse outcomes for both mother and foetus. No studies have been reported examining the prevalence, spectrum and management of thyroid disorders in pregnancy in the Black population of South Africa.

Objectives

To examine thyroid disorders in pregnancy at Chris Hani Baragwanath Academic Hospital (CHBAH) by assessing their underlying causes, management and outcomes, maternal and neonatal.

Methods

We performed a retrospective review of thyroid disorders in 88 patients, who attended the Antenatal Endocrine Clinic, from 2004 to 2008. All underwent initial and follow-up clinical and biochemical assessments. Delivery records were obtained where available. Thyroid function tests were performed on the neonates at least 48 hours after delivery.

Results

Fifty-eight (66%) of the 88 patients were hyperthyroid, 23(26%) were hypothyroid, and 7 (8%) had euthyroid endemic colloid goitres. Forty-eight (83%) of the 58 hyperthyroid patients had Graves' disease and, as such was the commonest thyroid disorder encountered. Overall it was estimated to be present in 0.06% of all pregnancies at CHBAH versus 0.2-0.4% reported by others. Almost half of the hypothyroid patients were due to I¹³¹ ablation for Graves' disease. Eighty percent of the Graves' disease and 83% of the hypothyroid patients were rendered euthyroid before delivery. A single fatal maternal outcome was due to uterine rupture. Six intra-partum foetal losses occurred. Among the newborns there was one case of a tracheo-oesophageal fistula and one of neonatal thyrotoxicosis.

Conclusion

This is the first report in Africa examining thyroid diseases in pregnancy. Thyroid disorders were less frequent than reported by others. Graves disease was the commonest disorder that presented to our Antenatal Endocrine Clinic.

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ABBREVIATIONS

ATD	antithyroid drugs
CHBAH	Chris Hani Baragwanath Academic Hospital
FT4	free thyroxine
FT3	free triiodothyronine
GD	Graves' disease
GTT	gestational transient thyrotoxicosis
IOM	Institute of Medicine
IUFD	intra-uterine foetal death
IUGR	intra-uterine growth restriction
hCG	human chorionic gonadotropin
HG	<i>hyperemesis gravidarum</i>
LBW	low birth weight
NHLS	National Health Laboratory Services
T4	thyroxine
T3	triiodothyronine
TBG	thyroxine-binding globulin
TG-Ab	thyroglobulin antibody
TSH	thyroid stimulating hormone
TPO-Ab	thyroid peroxidase antibodies
TRAb	thyroid stimulating hormone thyrotropin receptor autoantibody
WHO	World Health Organisation

Chapter 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1. Introduction

The management and outcomes of thyroid disease in pregnancy are determined by the physiological adaptations that normally occur during gestation. An understanding of these is necessary to optimally manage the variable disorders and achieve optimal outcomes. Over the past two decades, there has been a major proliferation of knowledge in this important field, given the deleterious effects of thyroid dysfunction for both mother and foetus and indeed later for the neurocognitive development of the child.

This literature review acts as the background to our retrospective study, which examines the underlying causes, management and outcomes of thyroid disorders in pregnancy.

Thyroid disease is a common endocrine disorder affecting women of reproductive age, second only to diabetes mellitus. It follows that thyroid disease in pregnancy is a frequently encountered clinical challenge. The reported prevalence of hyperthyroidism in the Western world is 0.1-0.4% of all pregnancies, Graves' disease (GD) accounting for the majority (85%) of cases. The prevalence of hypothyroidism is estimated to be 2.3-3.5%, with overt hypothyroidism accounting for 0.3-0.5% and subclinical hypothyroidism for 2-3%, in iodine-sufficient areas.^{1,2-4}

The importance of detecting and managing thyroid disease in pregnancy adequately is determined by the known adverse outcomes of untreated disease for both mother and foetus.⁵⁻⁶ The evaluation, diagnosis, and treatment in

pregnancy is determined by more strictly defined trimester-specific biochemical reference ranges.

1.2. Maternal thyroid physiology

Pregnancy is associated with changes in thyroid physiology to ensure an optimal thyroid environment for foetal growth and development. The overall effect of these changes is a requirement for increased maternal thyroid hormone production and secretion. Successful adaptation to these pregnancy-related alterations requires both a normally functioning thyroid gland and an adequate iodine intake.² During pregnancy, changes occur in thyroid physiology, which are reflected in the thyroid function tests.^{3-4,7-8}

1.2.1. Thyroxine-binding globulin, thyroxine, and triiodothyronine

Thyroid hormones are transported in serum non-covalently bound to three proteins, thyroxine-binding globulin (TBG), the major binding protein, albumin and transthyretin. Both the concentration of albumin and transthyretin remain stable throughout pregnancy, TBG, however, rises in early pregnancy and has doubled by 16-20 weeks gestation. Thereafter, its level is maintained until term.^{2,9} A major contributor to the raised TBG level is its reduced clearance, as well as its increased production in response to the hyper-oestrogenic state of pregnancy.¹⁰⁻¹¹ This leads to an increase in both serum total thyroxine (T4) and triiodothyronine (T3) concentrations. To maintain adequate free, unbound thyroid hormone concentrations during this period, free T4 (FT4) and free T3 (FT3) production by the thyroid gland increases to the extent of 50% above non-

pregnant levels. From 6-12 weeks gestation, T4 levels rise to 50% above non-pregnant reference ranges and plateau at mid-gestation. Total T3 levels rise and plateau later, at 20 weeks.²⁻³ These modifications represent the necessary adjustment from the preconception steady state to a “new” gestational equilibrium in the thyroidal economy.

1.2.2. Human chorionic gonadotropin

The human chorionic gonadotropin (hCG) molecule is a glycoprotein hormone secreted early in pregnancy by the syncytiotrophoblast, peaking at 9-11 weeks gestation and thereafter decreasing and has a weak thyroid-stimulating activity. This may contribute to modestly increased concentrations of serum FT4 and FT3, with reciprocally reduced serum TSH concentrations in 10-20% of healthy pregnant women. This transient, usually subclinical, hyperthyroidism is considered a normal physiologic finding.^{2,9,12}

1.2.2.1. Hyperemesis gravidarum

Hyperemesis gravidarum (HG) occurs in 0.5-10 per 1,000 pregnancies.¹³ It is characterized by a greater than 5% weight loss, dehydration and ketonuria. All the contributory factors are unknown but hCG certainly plays an important role. Thirty to 60% of these patients have elevated thyroid hormone levels and suppressed TSH in the absence of other common causes of thyrotoxicosis.¹⁴⁻¹⁵ A minority of these patients has clinical evidence of hyperthyroidism, better known as gestation transient thyrotoxicosis (GTT). The cause of excessive thyroidal stimulation is hCG itself, which, as mentioned, has intrinsic TSH

agonist activity.¹⁶ It usually resolves spontaneously with the declining hCG levels as pregnancy progresses.

1.2.3. Iodine

Iodine requirements are increased in pregnancy, due to both the higher maternal T4 production necessary to maintain maternal euthyroidism and an increased renal iodine clearance rate. Renal hyperfiltration and increased clearance of iodide begins early in pregnancy and persists until term, effectively causing obligatory iodine “leakage”. Later in pregnancy, the passage of iodine to the developing foetus via the foeto-placental unit further increases iodine requirements. The World Health organization (WHO) recommends an iodine intake in pregnant and lactating women of at least 200 µg/day. The Institute of Medicine (IOM) recommends 220µg/day.^{2,17}

1.2.4. Placenta and its regulation of thyroid hormone

The placenta contains a high concentration of the enzyme deiodinase 3, which effects inner-ring deiodination of T4 to reverse T3. This reduces the availability of T4 and T3 in the foetal circulation, and indirectly provides a source of iodide to the foetus. Circulating foetal T4 and T3 is mostly of maternal origin and is important for the development of a healthy foeto-maternal unit. In addition, the placenta actively transfers iodide to the developing foetus especially during the second half of gestation.¹¹

The outcome of all these adaptations is to successfully provide the developing foetus with adequate amounts of thyroid hormone, particularly during the first

trimester, as foetal thyroid hormone production only commences between the 12th to 14th weeks of gestation.⁷ Maternal euthyroxinaemia is important for normal foetal neurologic and somatic development.

1.3. Foetal thyroid physiology

The development and functioning of the foetal hypothalamic-pituitary-thyroid axis is dependent on the maternal-placental system for an adequate supply of iodide substrate. Foetal thyroid tissue and T4 synthesis are demonstrable by 10 weeks gestation following which there is progressive development of the hypothalamic-pituitary axis with an increase in serum thyrotropin levels and hence thyroid hormone synthesis.^{18,19} By term, foetal serum T4, T3 and TSH concentrations differ substantially from those in the mother, with TSH levels being higher and T4 and T3 levels being lower. Approximately 48-72 hours after delivery there is a TSH surge following which the levels fall. The serum T3 and T4 concentrations rise to levels higher than those in normal adults.⁷

1.4. Trimester-specific reference ranges in pregnancy

Given the alterations in gestational thyroid physiology, it is recommended that trimester-specific reference ranges for TSH and T4 be utilized, as maternal thyroid dysfunction may affect i) maternal health ii) foetal health and iii) obstetric and neonatal outcomes.⁸ Since 2007, much attention has been given to the development of such ranges.^{8,20-21}

Table 1: Trimester specific reference ranges

Trimesters	First	Second	Third
TSH (mIU/L)	0.1-2.5	0.2-3.0	0.3-3.0
T4 (nmol/L)	-	1.5-times the non-pregnant level	1.5-times the non-pregnant level

Given that TSH is suppressed by 20% to 50% during the first trimester owing to the thyrotropic activity of hCG concentrations, TSH levels may be misleading and are therefore not a reliable indicator of thyroid hormone sufficiency during the first trimester, unless trimester specific reference ranges are employed. By contrast, the second and third trimesters, TSH is the best measure of thyroid function.¹¹

T4 levels peak around mid-gestation with FT4 levels demonstrating a slight and temporary rise during the first trimester followed by a tendency to fall during later gestation. This fall is minimal (10%) in iodine-sufficient populations, but is exaggerated in iodine-deficient conditions (20-25%).² Interpretation of T4 during pregnancy is possible during the second half of gestation, with a value equal to 1.5 times the non-pregnant reference range.²² The interpretation of FT4 levels is variable depending on the assays and the laboratories used to measure them as well as the stage of gestation at which they are taken. No consensus has been reached worldwide on such 'pregnancy adapted' ranges, and hence it is advised that we exercise caution when interpreting FT4 in pregnancy.²²⁻²³

2.0 Thyroid disorders in pregnancy

2.1 Hyperthyroidism in pregnancy

Hyperthyroidism occurs in 2/1000 pregnancies. The most common cause is GD (85%).^{8,24-25} GTT (hCG-mediated) is even more frequently encountered than GD in pregnancy but is transient and confined to the first trimester. Other aetiologies such as thyroiditis, toxic multinodular goitre, toxic adenoma and iatrogenic hyperthyroidism are uncommon.

2.1.1 Gestational transient thyrotoxicosis

GTT results in transient, mild hyperthyroidism that is limited to the first trimester, and results from hCG stimulation of the TSH receptor.²⁶ The most common cause of this syndrome is HG (0.3-1.0% of all pregnancies).¹³ Uncommon causes are multiple pregnancies, hydatiform mole, choriocarcinoma and very rarely resistance to TSH hormone.^{16,27}

2.1.2 Graves' disease

GD may worsen during the first trimester, given the additive effect of hCG stimulating the TSH receptor. During the remainder of gestation the symptoms lessen as a result of the immunologic alterations that occur in pregnancy.^{8,28}

2.1.3 Clinical presentation

Hyperthyroidism during pregnancy may not be clinically apparent, as many of the signs and symptoms are similar to those of the normal physiologic changes

that accompany pregnancy, such as mild palpitations and heat intolerance. Clinical clues that increase the likelihood of autoimmune hyperthyroidism include symptoms antedating conception, the presence of other autoimmune conditions or the presence of a goitre and ophthalmopathy.²²

2.1.4 Laboratory testing

In the setting of absent clinical features and negative thyroid antibodies, GD may be difficult to differentiate from the other causes of hyperthyroidism²⁹ as radioisotope scanning is absolutely contraindicated during pregnancy.

Diagnosis of hyperthyroidism is confirmed in the usual manner by finding a suppressed TSH and elevated FT4 levels, employing trimester-dependent normal values for TSH as previously discussed. Markers of thyroid autoimmunity are essential in the evaluation of hyperthyroidism in pregnancy. These include, thyroid peroxidase antibodies (TPO-Ab), which are elevated in two thirds of patients with GD, thyroglobulin antibodies (TG-Ab), and the most specific for GD, thyroid-receptor antibodies (TRAb).³⁰⁻³¹

2.1.5 Complications

Meticulous treatment of hyperthyroidism is necessary to prevent maternal, obstetric and foetal complications as uncontrolled hyperthyroidism secondary to GD is associated with i) increased risk of miscarriage, ii) pre-term delivery, iii) pregnancy-induced hypertension,³² iv) low birth weight,³³ v) intra-uterine growth restriction, vi) stillbirth,⁶ vii) thyroid storm and viii) maternal congestive cardiac failure.³⁴⁻³⁵

2.1.6 Management

GTT is self-limiting and best managed with supportive treatment such as intravenous fluids¹⁵ Antithyroid (ATD) drugs are not indicated in most cases. Treatment with beta-adrenergic blockers is effective in controlling the symptoms.

When managing patients with GD in pregnancy, there are three clinical situations that are important to consider: a) women with active pre-existing GD and who are on ATD, b) women who have had GD and who are now in remission and c) women with GD which is newly diagnosed in pregnancy. In all cases measuring maternal TRAb concentrations is helpful in evaluating the risk of foetal hyperthyroidism, which occurs in 1-5% of neonates born to mother with GD.³⁶ These antibodies in high titres readily cross the placenta beginning in the late second trimester. Levels should be measured by 24-28 weeks gestation and, if found to be at least three-times the upper normal limit, may indicate a potential foetal risk and should be closely monitored. Early signs of the disease in the foetus include the presence of a foetal goitre³⁷ and tachycardia (heart rate >160bpm). Later signs include intrauterine growth restriction (IUGR), oligohydramnios, *hydrops foetalis* and accelerated bone maturation.²²

ATD are the treatment of choice, using the lowest possible dose necessary to maintain the FT4 in the upper third of the reference range.²³ Propylthiouracil, methimazole and carbimazole are all equally effective and able to cross the placenta.³⁸ The usage of methimazole /carbimazole in the first trimester of pregnancy may be associated with *aplasia cutis* and a condition known as “methimazole embryopathy” which consists of choanal or oesophageal atresia

and dysmorphic facies.³⁹⁻⁴⁰ Given these concerns, propylthiouracil is the preferred drug of choice during the first trimester.⁸ As propylthiouracil carries with it an increased risk of fulminant hepatotoxicity,⁴¹ it is recommended that this agent be terminated at the end of the first trimester and substituted with methimazole/carbimazole. The requirement for ATD's decreases during the second half of gestation, and 30-40% of patients become and remain euthyroid.³¹ Radioiodine is absolutely contraindicated during pregnancy.⁴² Thyroidectomy during the second trimester may be rarely necessary. It is an option for women who are intolerant of thionamides owing to allergy, agranulocytosis, or other major side effects.

2.2 Hypothyroidism in pregnancy

2.2.1 Prevalence and causes

Overt hypothyroidism complicating pregnancy is unusual (0,3-0,5%),⁴³ as most of these women are anovulatory. Furthermore, the risk of first trimester miscarriages is high.⁴⁴ Subclinical hypothyroidism (raised TSH and a normal or low normal FT4) is more commonly encountered (2-5% of pregnancies).^{43,45} Fifty to 60% of these patients will have evidence of thyroid autoimmunity (TPO-Ab and or TG-Ab) in iodine sufficient populations i.e. Hashimoto's disease.⁸

Worldwide, the most important cause of maternal thyroid deficiency remains iodine deficiency, known to affect 1.2 billion individuals.⁴⁶ The most common cause of hypothyroidism in iodine-sufficient pregnant and non-pregnant females

is Hashimoto's disease.^{4,11} Other causes include previous radioiodine or surgical ablation of the thyroid gland.

2.2.2 Clinical presentation

The clinical features are similar to those in the non-pregnant state but are often subtle. The majority of patients are asymptomatic.⁴⁷ The presence of anti-thyroid peroxidase antibodies assists in diagnosing the underlying cause. A high index of suspicion is required, especially in women with a predisposition to thyroid disease such as a personal or family history of thyroid disease and the coexistence of other autoimmune disorders.¹¹

2.2.3 Laboratory testing

The diagnosis is confirmed on biochemical testing, upon finding an elevated serum TSH concentration, defined using trimester-specific TSH reference ranges for pregnant women. Overt hypothyroidism is defined as a low FT4 plus an elevated TSH concentration. Subclinical hypothyroidism is defined as an elevated trimester-specific serum TSH concentration and a normal FT4 concentration.^{1,47}

2.2.4 Complications

Untreated maternal hypothyroidism has been found to have adverse consequences for both mother and foetus. The critical role of thyroid hormone in foetal brain development can explain the increased risk of neuropsychological impairment in the foetus of mothers with subclinical hypothyroidism. Pre-

eclampsia, preterm delivery, low birth weight, perinatal morbidity/mortality and impaired neurologic development may complicate overt hypothyroidism.^{5,44}

2.2.5 Management

Treatment consists of optimizing thyroxine requirements pre-conception and adjusting thyroxine therapy as appropriate during pregnancy. The goal is to restore a euthyroid state as soon as possible. Fifty to 85% of women with pre-existing hypothyroidism require higher doses of thyroxine replacement during pregnancy.^{44,48-50}

In general, women who have undergone thyroid ablation require higher replacement doses than those with Hashimoto's thyroiditis, where there still may be some residual thyroid function. It is important to initiate treatment as soon as the diagnosis is made. The goal of treatment is to maintain a TSH levels in the lower half of the trimester-specific reference range and a FT4 in the upper half of the reference range. Postpartum, the dose of thyroxine should revert to the pre-pregnancy level, with thyroid function testing being performed 6 weeks following delivery.^{11,22}

Evidence for the use of thyroxine in subclinical hypothyroidism is less secure, with differing recommendations among various professional organisations, and is beyond the scope of this review.^{47,51}

In conclusion, the thyroid gland is substantially challenged during pregnancy, most notably in areas of iodine deficiency. Thyroid disorders are common in women of childbearing age.⁴

3.0 Study aims and objectives

3.1 Aims

The aim of this study is to evaluate the prevalence and spectrum of thyroid disease in pregnancy at the Chris Hani Baragwanath Academic Hospital Antenatal Endocrine Clinic. In addition, we aim to assess the underlying causes, control and management thereof, as well as the maternal and neonatal outcomes using clinical and biochemical parameters. To date, there have been no such studies in our population.

3.1 Objectives

1. To determine the prevalence of thyroid disease in pregnant females attending the Antenatal Endocrine Clinic at Chris Hani Baragwanath Academic Hospital.
2. Determine the causes, control, and management of thyroid disease in this cohort.
3. To differentiate and compare hyperthyroid and hypothyroid disease during pregnancy.
4. Furthermore to compare pre-gestational thyrotoxicosis versus gestational thyrotoxicosis
5. To evaluate maternal and neonatal outcomes of thyroid disease during pregnancy

3.3 Methods

3.3.1 Study design

This is a retrospective review of the patients who attended the Antenatal Endocrine Clinic during the period January 2004 to April 2008.

3.3.2 Study population

3.3.2.1 Site of study

Chris Hani Baragwanath Academic Hospital, Antenatal Endocrine Clinic.

3.3.2.2 Size

All thyroid patients that attended the clinic between January 2004 and April 2008 - 88 patients were identified. The total number of antenatal patients attending the Chris Hani Baragwanath Maternity clinic during this time was estimated at 92 000. As a tertiary centre, patients were also referred from outlying clinics. Patients had either a previously existing or a newly diagnosed thyroid disorder. Being a descriptive study, no sample calculation was made. Only patients who fulfilled the biochemical criteria according to trimester specific reference ranges for thyroid disease were included.

3.3.2.3 Measurements and observations

- Maternal characteristics
 - a) Age
 - b) Parity and gravida

- c) Weight at first and subsequent bookings
- d) Gestational age at first- and subsequent visits
- e) Blood pressure at first and subsequent visits
- Cause of thyroid disease:
 - a) Hyperthyroidism: GD or thyrotoxicosis from other causes.
 - b) Hypothyroidism: Hashimoto's disease or post-radioactive iodine therapy.
- Whether persistent thyroid disease or newly diagnosed during pregnancy
- Thyroid drug therapy: carbimazole or thyroxine replacement therapy:
 - a) Currently on, or newly initiated during course of pregnancy?
 - b) Dose of drug at each visit
- Whether previously received radioactive iodine?
- Laboratory investigations, recording of:
 - a) Thyroid function testing, including thyrotropin (TSH) and free thyroxine (T4), monitored monthly
 - b) Thyroid antibodies: antimicrosomal (TPO-Ab) and antithyroglobulin (TG-Ab)
- Recording of outcomes for mother
 - a) Date and mode of delivery
 - b) Maternal outcome: delivered, intra-uterine foetal death, spontaneous abortion or molar pregnancy
 - c) Thyroid function tests pre-delivery
- Recording of demographics and outcomes for the infant
 - a) Gestational age at delivery
 - b) Gender: male or female

c) Weight

d) Apgar scores taken at 1 and 5 minutes

- Presence of foetal anomalies:
 - Thyroid disease/ drug related
 - Other
- Thyroid function test results at various intervals post- delivery

An extensive data sheet recording all the variables mentioned is attached.

(Appendix 3.1)

3.3.2.4. Limitations and/or confounding variables

Limitations of this study include:

- few mothers and/or infants lost to follow-up
- mothers who delivered elsewhere

Currently, a separate prospective study at our institution of a similar nature, including patients from 2008 onwards, is being conducted and therefore data will only be analyzed until 2008.

3.4 Data analysis

The data obtained shall be entered into a database, which will be analyzed using descriptive analysis techniques in consultation with a statistician. Data will be processed using Statistica version 10.0 statistical software. A descriptive analysis will be carried out for categorical variables, where frequencies and percentages will be computed while means and standard deviations will be used for numerical variables. For data that is not normally distributed, medians

and interquartile ranges will be used. Statistical significance will be considered to be a p-value of <0.05.

3.5 Ethics

An application has been made to the Wits Human Research Ethics Committee, with submission of application on 1st August 2012.

Permission to retrieve and utilize the data will be requested from Chris Hani Baragwanath Academic Hospital management, once ethics has been approved.

Permission from the Head of Department of Medicine and the Antenatal Endocrine clinic has already been received.

3.6 Timing

Detailed analysis will commence once ethics approval has been granted.

The expected duration is depicted below.

	July 2012	August	Sep	Oct	Nov	Dec	Jan	Feb 2013
Literature review	✓	✓						
Preparing protocol	✓	✓						
Protocol assessment			✓					
Ethics approval				✓				
Collecting data					✓	✓		
Data analysis							✓	✓
Writing up thesis							✓	✓

3.7 Funding

No costs are anticipated other than that necessary for stationery, photocopying, printing, and binding which will be covered by myself.

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CHAPTER 2: SUBMISSIBLE ARTICLE

A Retrospective Analysis of Thyroid Disease in Pregnancy at the Chris Hani Baragwanath Academic Hospital, Soweto, South Africa

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ABSTRACT

Background

Hyperthyroidism occurs in 0.1-0.4% of pregnancies, Graves' disease accounting for 85% of cases. Hypothyroidism occurs in 2.3-3.5% of pregnancies, of which overt hypothyroidism accounts for 0.3-0.5% and subclinical hypothyroidism for 2-3%. Thyroid disease in pregnancy is known to be associated with adverse outcomes for both mother and foetus.

No studies have been reported examining the prevalence, spectrum and management of thyroid disorders in pregnancy in the Black population of South Africa.

Objectives

To examine thyroid disorders in pregnancy at Chris Hani Baragwanath Academic Hospital (CHBAH) by assessing their underlying causes, management and outcomes, maternal and neonatal.

Methods

We performed a retrospective review of thyroid disorders in 88 patients, who attended the Antenatal Endocrine Clinic, from 2004 to 2008. All underwent initial and follow-up clinical and biochemical assessments. Delivery records

were obtained where available. Thyroid function tests were performed on the neonates at least 48 hours after delivery.

Results

Fifty-eight (66%) of the 88 patients were hyperthyroid, 23(26%) were hypothyroid, and 7 (8%) had euthyroid endemic colloid goitres. Forty-eight (83%) of the 58 hyperthyroid patients had Graves' disease and, as such was the commonest thyroid disorder encountered. Overall it was estimated to be present in 0.06% of all pregnancies at CHBAH versus 0.2-0.4% reported by others. Almost half of the hypothyroid patients were due to I¹³¹ ablation for Graves' disease. Eighty percent of the Graves' disease and 83% of the hypothyroid patients were rendered euthyroid before delivery. A single fatal maternal outcome was due to uterine rupture. Six intra-partum foetal losses occurred. Among the newborns there was one case of a tracheo-oesophageal fistula and one of neonatal thyrotoxicosis.

Conclusion

This is the first report in Africa examining thyroid diseases in pregnancy. Thyroid disorders were less frequent than reported by others. Graves disease was the commonest disorder that presented to our Antenatal Endocrine Clinic.

Introduction

Thyroid disease is a common endocrine disorder affecting women of reproductive age such that thyroid disease in pregnancy is a frequently encountered clinical challenge. Pregnancy poses a significant challenge to the thyroid economy, particularly in iodine-deficient mothers. Over the past two decades, there has been a major increase in information regarding thyroid disorders in pregnancy.¹⁻⁶

The reported 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%), and that of hypothyroidism estimated to be 2.3-3.5%, of which overt hypothyroidism accounts for 0.3-0.5% and subclinical hypothyroidism for 2-3% in iodine-sufficient areas.^{1,2,7}

The importance of thyroid disease in pregnancy is determined by the known adverse outcomes of untreated disease for both mother and the foetus.⁸⁻¹⁴

While the evaluation, diagnosis and treatment is similar to that in the non-pregnant state, pregnancy presents unique challenges.

The profound changes that occur in thyroid physiology reflect an increased demand by both mother and foetus for thyroid hormone. This is reflected in the altered thyroid function tests that occur during the gestational period. Key changes include the increase in serum thyroxine-binding globulin (TBG) a consequence of the hyperoestrogenic state,¹⁵ stimulation of the TSH receptor by human chorionic gonadotropin (hCG),¹⁶ and the increased demand for iodine

owing to increased maternal thyroid hormone production and iodide clearance rates.^{2,17}

Data from a 2001 study demonstrated that more than a third of the South African population are still iodine deficient, as reflected by the fact that endemic goiter remains the most prevalent thyroid disorder among all South Africans.¹⁸

Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, is the largest hospital in Africa and serves a large, predominantly disadvantaged urban black population.

Regarding thyroid disorders in pregnancy in the black South Africa population, there is a lack of published data regarding its prevalence, presentation, management and outcomes.

Aims

To evaluate the spectrum of thyroid diseases in pregnancy at CHBAH in Soweto by examining and assessing their underlying causes, control and management. In addition, maternal and foetal outcomes were assessed.

Materials and Methods

1. Study population

We retrospectively reviewed 88 patients presenting to our Antenatal Endocrine Clinic from January 2004 to April 2008. All women were referred to the clinic by the 10 decentralised antenatal clinics in Soweto, clinics from the surrounding areas as well as the CHBAH own antenatal clinic and the Adult Endocrine

Clinic. The patients referred included both those with pre-existing thyroid diseases and those in whom a diagnosis of a thyroid disease was made for the first time during pregnancy. A multidisciplinary team consisting of an obstetrician, endocrinologist and nurse educator saw patients fortnightly.

2. Data collection

All patients underwent an initial assessment, which included documenting maternal characteristics, such as age, parity, duration of gestation and the causes of the thyroid disorder. Baseline assessments included serum thyrotropin (TSH), free thyroxine (FT4) concentrations, antimicrosomal antibodies (TPO-Ab) and antithyroglobulin antibodies (TG-Ab).

Patients were classified as having GD if they had a previous history of known GD or were biochemically hyperthyroid with evidence of ophthalmopathy, dermopathy or thyroid antibody positivity, or any combination thereof. FT4 and TSH were monitored every four weeks and treatment was adjusted as necessary.

The delivery records of the mothers were obtained where available and thyroid function testing was performed on the neonates at or after 48 hours of age. The maternal outcomes recorded included, Caesarian section rates, maternal complications, spontaneous miscarriage and intra-uterine foetal deaths (IUFD). The adverse foetal outcomes noted were those of low birth weight (LBW), premature delivery and congenital abnormalities.

It must be pointed out that not all mothers delivered their infants at the CHBAH, as some delivered at peripheral hospitals or clinics or at home.

3. Assays

The analyses of blood serum samples were performed by the South African National Health Laboratory Services (NHLS). The FT4 and TSH concentrations were measured by an automated two-step electrochemiluminescence-immunoassay (Cobas, Roche Diagnostics GmbH, Mannheim, Germany). Adult reference ranges were as follows; TSH 0.35-4.5mIU/L, FT4 11-21pmol/l. The following trimester specific TSH reference ranges were utilised for this study: 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. We made use of a non-pregnant FT4 reference range since our laboratory has not established trimester specific reference ranges. The limit of detection for TSH was 0.005 mIU/L and 0.300 pmol/L for FT4. The 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, Europe, Dartford, United Kingdom).

If a patient had more than one TSH and FT4 test done in each trimester, the median (interquartile range) for the trimester 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 either classified as being either hypothyroid or hyperthyroid. In the rare event that the TSH was normal and the FT4 minimally elevated, the patient was regarded as being euthyroid. When the TSH was subnormal and the FT4 normal, we relied on the TSH as a being the more reliable measure of thyroid function, except during the first trimester where it is known that TSH levels may be suppressed up to <0.01mIU/L. For foetal TSH and FT4 levels the following

reference ranges were used, as adapted from our laboratory (for a neonate between 2 and 5 days of life): TSH 0.7-15.2 mIU/L and FT4 11-32 pmol/L

4. Definitions

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

IUFD was assessed to be a foetus had that demised following the 26th week of gestation.

A spontaneous miscarriage was defined as a spontaneous loss of conceptus prior to 26 weeks pregnancy or one in which the mass was less than 600grams.

Premature delivery was considered to be any delivery occurring prior to the 37th week of gestation.

LBW was defined as a foetal weight below 2500 grams.

A low Apgar score was defined as a mean foetal score of equal to or less than 7 points at 5 minutes.

Thyroid antibody status was considered positive if either TPO-Ab or TG-Ab test were positive

5. Statistical analysis

Values are presented as either means \pm SD for normally distributed data, or else as medians and interquartile ranges (IQRs) with categorical variables expressed as percentages. Differences between groups were assessed using the chi-squared test for the categorical variables and with the t-test and

Wilcoxon-Mann-Whitney test for normally and non-normally distributed continuous variables respectively. Results were taken as statistically significant for p-values of less than 0.05.

Results

In the current study, in which 88 patients with thyroid disorders were retrospectively identified and reviewed over a four-year period, the frequency of thyroid disease was 0.09%. This was established on a background of approximately 92 000 women attending the general antenatal clinic at CHBAH. The frequency of GD and overt hypothyroidism were 0.06% and 0.04% respectively.

Maternal demographics and thyroid status

The mean age of the 88 patients at presentation to the Antenatal Endocrine Clinic was 29 years (± 5.8) and their mean duration of gestation was 19.8 weeks (± 8.5). Fifty eight (66%) patients were hyperthyroid (either predating the pregnancy or newly diagnosed during the pregnancy), 23 (26%) were hypothyroid and 7 (8%) were euthyroid, with a colloid goitre. Sixty eight (77%) patients had known thyroid disease, whereas the remaining 20 (23%) were detected for the first time during pregnancy. Thyroid antibody status, including anti-thyroid peroxidase (TPO-Ab) and anti-thyroglobulin (TG-Ab) were only available for 42 (48%) of the patients. Of these 13 (31%) patients tested positive and 29 (69%) tested negative (Table 2). The underlying cause for their thyroid disorders is given in Table 3.

Patients with hyperthyroidism (n=58)

Of the 58 patients with hyperthyroidism, 48 (83%) had GD, 9 (16%) were classified as gestational thyrotoxicosis and one patient had a molar pregnancy. Thyroid biochemistry profiles for the groups at presentation and delivery are depicted in Table 4.

a) Graves' hyperthyroid patients (n=48)

The mean age of all the hyperthyroid GD patients was 28 years (± 5.7) and their mean age at presentation was 19 weeks (± 8.8) gestation. The antibody status was known in 28 of all the GD patients: 10 (36%) were positive and 18 (64%) were negative. Thirty-eight (79%) of the 48 patients with GD had known preexisting disease and 10 (21%) were newly diagnosed with Graves' hyperthyroidism in pregnancy. Characteristics of the GD group are shown in Table 5.

Of 40 thyroid function tests available at delivery for the GD group as a whole, 32 (80%) were rendered biochemically euthyroid by the time of delivery i.e. three (50%) out of the 6 available results in the newly diagnosed group and 29 (85%) out of the 34 available results in the preexisting group being euthyroid at delivery. Figures 1 and 2 demonstrate the median TSH (mIU/l) and FT4 (pmol/L) by week of pregnancy for both preexisting and newly diagnosed GD patients.

b) Non GD hyperthyroid (n= 10)

The mean age of the remaining 10 hyperthyroid patients at presentation was 29 years of age (± 6.0) and their mean gestational age at first presentation was 18 weeks (± 8.1). This group consisted of: *hyperemesis gravidarum* three, molar pregnancy one, unknown four, and the remaining two were lost to follow-up at an early stage. The thyroid antibodies were negative in those patients for whom a result was available (4/10).

Patients with Hypothyroidism (n= 23)

The mean age at presentation of the 23 hypothyroid patients was 31 years (± 5.6) and the mean gestational age was 21 weeks (± 8.2). The majority 12 (52%) of the patients were former GD patients who had been ablated with radioiodine. Six (26%) patients followed thyroidectomy and 4 (17%) patients had confirmed Hashimoto's disease. One patient had congenital hypothyroidism. Of the patients who had a thyroidectomy (n=6), 2 were for thyrotoxicosis, one was for papillary thyroid cancer, and one for the prophylactic management of familial medullary thyroid carcinoma. The indication for thyroid diseases in the remaining the two thyroidectomies had not been documented. Eighteen patients had thyroid function results available at delivery of which 15 (83%) were euthyroid. Thyroid biochemistry profiles at presentation and delivery are depicted in Table 4.

Patients with a Euthyroid colloid goiter (n=7)

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

Maternal/ Obstetric outcomes (n=56)

There was one maternal death in a patient with a euthyroid goiter, secondary to uterine rupture at term following an induction of labour at 38 weeks. There were seven mothers with documented cardiac failure at first presentation, all in patients with GD, most of these i.e. four were in the newly diagnosed group, and three in the pre-existing group. One of the mothers with newly diagnosed GD remained thyrotoxic throughout her pregnancy and she had a spontaneous miscarriage at 26 weeks gestation. A second mother in the pre-existing GD group who was biochemically euthyroid, miscarried at 13 weeks of pregnancy. The delivery records were available for 56 (68%) of the successful pregnancies (n=82). However, details were not available for 26 (32%) of the patients, as they had been lost to follow-up. There were six foetal losses, four of which were IUFD and two spontaneous miscarriages. (Table 6) The majority of deliveries n=49 (88%) occurred at term (overall median (IQR): 38 (37-40) weeks) with a total of 7 (12%) premature deliveries. Maternal outcomes for the hyperthyroid and hypothyroid groups are shown in Table 6.

Foetal outcomes (n=56)

Of all the delivered newborns, 80% (n=43) had a normal birth weight (overall mean weight 2895 ± 495 gm). Eleven neonates (20%) had LBW (<2500gm) of which four of these were premature deliveries. Most (nine) of the mothers with LBW babies had GD, seven were euthyroid at delivery and two were hyperthyroid at delivery. The remaining two were patients from the hypothyroid group who were biochemically hypothyroid at delivery.

There was one instance of a macrosomic baby (4030 grams) born to a mother with a euthyroid colloid goitre and no other co-morbidities. Overall, the neonates born to the mothers who were hypothyroid (n=12) tended to be larger, (mean weight 3017 ± 496 gm) however this was not significantly different from the hyperthyroid group. Table 7. Apgar scores were similar in the hyper- and hypothyroid groups (medians of 9 and 10 at 1 and 5 minutes respectively in both groups). Two neonates born to mothers in the hyperthyroid group (n= 38) had initial Apgar scores of 7, which improved to normal after 5 minutes. One neonate born to a mother in the hypothyroid group (n=12) had an initial Apgar of 4 and a repeat of 6. There was no obvious explanation for this, as the baby was a full-term delivery, and the mother had been euthyroid throughout gestation.

Thyroid functions in 35 neonates were all normal except for one case of neonatal thyrotoxicosis, which was reconfirmed at 3 weeks of age (TSH=0.01mIU/L and FT4 >100pmol/L). Two neonates were born with congenital anomalies. One had polydactyly, and the other a trachea-oesophageal fistula (TOF). There was one baby who died in the early neonatal period as a result of gastroenteritis.

Discussion

Thyroid disease in pregnancy has remained an area of public health concern with several clinical guidelines addressing this very issue.¹⁹⁻²¹

To date, there are very few epidemiological studies assessing prevalence of thyroid disease in pregnancy. This is the first comprehensive report from Africa of thyroid disorders in pregnancy.

In our cohort of 88 patients, sixty patients had either a prior history of GD or were newly diagnosed at the Antenatal Endocrine clinic. Not surprisingly, GD was by far the most common thyroid disorder encountered in pregnancy. Our frequency of 0.06% of all pregnancies was lower than the 0.2-0.4% reported by others.²²⁻²³ While this may reflect a lower prevalence of GD in our population, it is possible that some patients were misclassified as having gestational thyrotoxicosis, rather than GD based on their negative thyroid antibody status in 64% and lack of clinical features. In addition, availability of TRAb testing in our hospital laboratory was not available.

The frequency of GTT in our cohort was a mere 0.008%, which was profoundly less than the figure of 2-11%.²⁴⁻²⁵ This is likely due to the fact that the mean gestational age at first presentation was 20 weeks, i.e. well beyond the first trimester.

Hashimoto's thyroiditis was relatively uncommon. This disease is known to be rare in Black South Africans.²⁶ In any event Hashimoto's disease is not common in women of childbearing age.

The frequency of thyroid antibody positivity of 36%, in our patients with GD is much lower compared to published first world data for non-pregnant individuals.²⁷⁻³⁰ Few studies have evaluated thyroid antibody status in healthy African patients.³¹⁻³⁷ It has however been established that thyroid antibody levels fall progressively in pregnancy in healthy women without a thyroid disorder.³⁸⁻³⁹ This can be attributed to the immune privileged state.⁴⁰⁻⁴¹ In this respect, it should be noted that the majority of our GD patients first presented well into the second trimester. Other factors could have contributed to the low prevalence of thyroid antibodies. Iodine insufficiency may have played a role.⁴² This finding may also have been subject to selection bias, given the small sample size. Finally, the thyroid antibodies were measured using a now outdated passive agglutination assay with a poor sensitivity and specificity. Overall our patients were satisfactorily controlled, 86% having been rendered euthyroid by the time of delivery.

The mean TSH levels of 0.03 in the preexisting GD group, is normal for the early stages of pregnancy, given the effect of hCG and is consistent with the normal FT4 level of 15.7mmol/L. However, nearly half the patients were hyperthyroid at first attendance at the Antenatal Endocrine Clinic but by the time of delivery, good clinical and biochemical control had been achieved as reflected in the normal TSH and FT4 values (Table 5).

In those patients with newly diagnosed GD, the majority presented late in the course of their pregnancies i.e. mean of 22.6 weeks. All were thyrotoxic at first presentation with over half (66%) being rendered euthyroid by delivery. It

should be noted that results were only available for six out of the ten patients in this group.

Six adverse obstetric outcomes occurred, four IUFDs and two spontaneous abortions. Two of the IUFDs occurred in patients who had GD. One mother presented in the late second trimester with newly diagnosed GD and was found to have acute polyhydramnios with *hydrops foetalis* at presentation. The other had preexistent GD and was inadvertently given radioiodine for a thyroid scan during early pregnancy. Of the two remaining IUFDs, one occurred in a hypothyroid mother with pseudohypoparathyroidism and the other in a euthyroid mother who had a history of ongoing late pregnancy losses and ruptured her uterus following induction of labour. She subsequently demised.

Of all the neonates born at CHBAH itself (n=56), one early neonatal death occurred and was attributed to gastroenteritis. While the majority of the neonates delivered were of normal weight (mean 2895gm), 20% were born with a LBW. Four of these were born to mothers who were either hyper- or hypothyroid at the time of delivery. In our cohort other reasons for the LBW might be poor nutrition and underlying chronic diseases such as human immunodeficiency virus, which was not accounted for in our study.

There was one instance of neonatal thyrotoxicosis. This infant was born to a mother who presented for the first time at 24 weeks gestation with newly diagnosed GD during pregnancy (TSH 0.01 and FT4 60.8pmol/L). She was treated with carbimazole 60mg daily but then defaulted. Two neonates had congenital anomalies, one had polydactyly, a common anomaly found in the

Black South African population and another had a TOF. This abnormality is one of those which may occur as part of a postulated “methimazole embryopathy.”⁴ We recognize that our study has certain inherent limitations. These include the retrospective nature of the study and the relatively small number of patients, and the fact that some patients were lost to follow up. It should be noted that we do not perform routine screening for thyroid disease in pregnancy but rely on case finding. In addition, iodine status was not assessed and TRAb levels were not measured.

Way forward

Despite the limitations of this study, our findings add valuable epidemiological information to the paucity of data that exists for thyroid disease in pregnancy in sub-Saharan Africa.

In the future, we plan to conduct a prospective study identifying and evaluating the prevalence, behavior of, as well as maternal and foetal consequences of thyroid disease in pregnancy with patients being identified by screening high-risk individuals. In addition, we aim to derive trimester-specific reference intervals for TSH and FT4 in our pregnant population group.

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Nil

Disclosure statement

The authors have no conflict of interest to declare

Table 2: Maternal demographics

	All patients n= 88	Hyperthyroid n=58	Hypothyroid n=23	Euthyroid colloid goitre n= 7
Age (years)	29.0 ± 5.8	27.9 ± 5.8	30.9 ± 5.6	31.4 ± 5.4
Gestational age at presentation (weeks)	19.8 ± 8.5	18.8 ± 8.6	21.0 ± 8.2	24.1 ± 7.3
Preexisting 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)

All continuous variables are expressed as means ± standard deviations (SD)

*Results for thyroid antibodies (TPO-Ab and TG-Ab) were only available for 42 of the 88 patients, 32 in the hyperthyroid group, 6 in the hypothyroid group and 4 in the euthyroid group

Table 3: Distribution of the thyroid disorders

	Number of patients n=88	Percent (%)
Hyperthyroid group	58	(66)
Graves' disease	48	82.7
Gestational thyrotoxicosis	9	15.5
Molar pregnancy	1	1.7
Hypothyroid group	23	(26)
Post I-131 treatment	12	52.2
Post thyroidectomy	6	26.1
Hashimoto's disease	4	17.4
Congenital hypothyroidism	1	4.4
Euthyroid goitre	7	(8)

Table 4: Thyroid function test of each group to the Antenatal Endocrine clinic at presentation and delivery

	All patients	Hyperthyroid	Hypothyroid	Colloid goiter
At first presentation	n= 87	n=57	n=23	n= 7
TSH (mIU/L)	0.38 (0.01-2.42)	0.02 (0.01-0.45)	7.36 (1.56-16.89)	1.02 (0.06-1.32)
FT4 (pmol/L)	14.6 (11.8-32.8)	23.8 (12.9-44.1)	11.0 (7.0-14.3)	13.0 (10.9-15.1)
Patients euthyroid n (%)	34 (39)	21(36)	6 (30)	7(100)
At delivery	n=70	n=46	n=18	n=6
TSH (mIU/L)	1.03 (0.14-2.38)	0.96 (0.01-2.01)	1.85 (0.57-3.35)	0.89 (0.44-1.25)
FT4 (pmol/L)	13.2 (11.9-15.1)	13.1 (11.9-14.4)	14.1 (12.3-15.9)	13.0 (9.4-15.2)
Patients euthyroid %	86 (60/70)*	85 (39/46)*	83(15/18)*	100(6/6)*

All variables are expressed as medians and interquartile ranges (IQR)

* Thyroid function results available in 69 patients, 45 in the hyperthyroid group, 18 in the hypothyroid group, 6 in the euthyroid group, 18 having been lost to follow-up.

Table 5: Characteristics of patients with Graves' disease

	Preexisting GD n=38	Newly diagnosed GD n=10	p-value
Age (years)	28.2 ± 5.4	25.6 ± 6.9	0.205*
GA (weeks)	17.9 ± 8.9	22.6 ± 7.9	0.141*
At presentation	n=38	n=10	
TSH (mIU/L)	0.03 (0.01-1.1)	0.01(0.01-0.01)	0.036 [#]
FT4 (pmol/L)	15.7 (12.1-41.0)	69.8 (60.8-100)	<0.001 [#]
At delivery	n=33	n=6	
TSH (mIU/L)	1.19 (0.03-1.86)	0.01 (0.01-2.01)	0.323 [#]
FT4 (pmol/L)	13.2 (11.9-14.4)	15.3 (9.8-60.8)	0.414 [#]

Normally distributed continuous variables are expressed as means ± standard deviations (SD); TSH and FT4 levels were not normally distributed and thus are expressed as medians and interquartile ranges (IQR)

*p-values for age and GA calculated using a t-test

[#]p-values for TSH and FT4 levels calculated using the Wilcoxon-Mann-Whitney test

Table 6: Maternal outcomes of patients that delivered at CHBAH

	All patients n=56	Hyperthyroid n=40	Hypothyroid n=12
Caesarian section n (%)	9(16)	7(18)	2(17)
Premature deliveries n (%)	7(12)	5(13)	2(17)
IUFD n (%)	4(7)	2(5)	2(17)
Spontaneous abortions n (%)	2(4)	2(5)	0
Molar pregnancy n (%)	1(6)	1(3)	0

Table 7: Neonatal outcomes of babies that delivered at CHBAH

	All patients n=56	Hyperthyroid n=40	Hypothyroid n=12	p value*
GA at delivery (weeks)	38.1 ± 2.0	38.1 ± 2.1	37.7 ± 1.9	0.520
Birth weight (grams)	2895 ± 495	2836 ± 479	3017 ± 496	0.275
No. with LBW <2500gm n (%)	11 (20%)	9 (23%)	2 (17%)	0.758
No. with a congenital abnormality	2	2 [#]	0	

All continuous variables are expressed as means ± standard deviations (SD)

*p-values calculated using a t-test comparing the hyperthyroid and hypothyroid groups

[#]Tracheo-oesophageal fistula and polydactyly

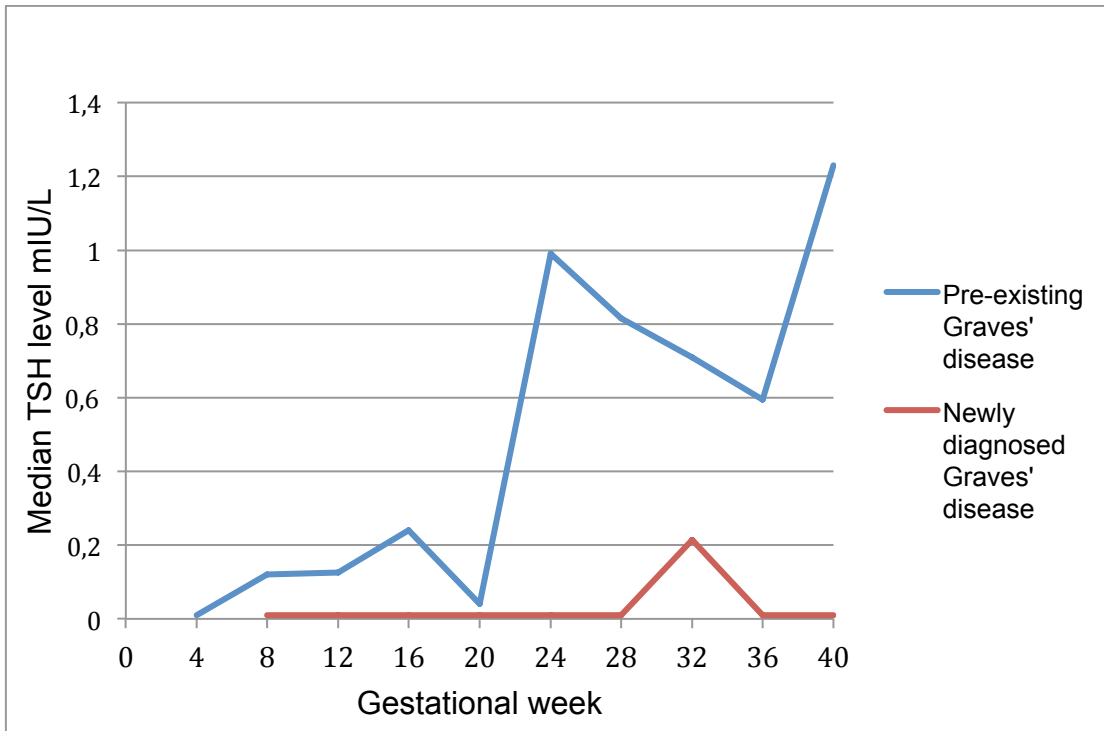


Figure 1: Median TSH levels by week of pregnancy

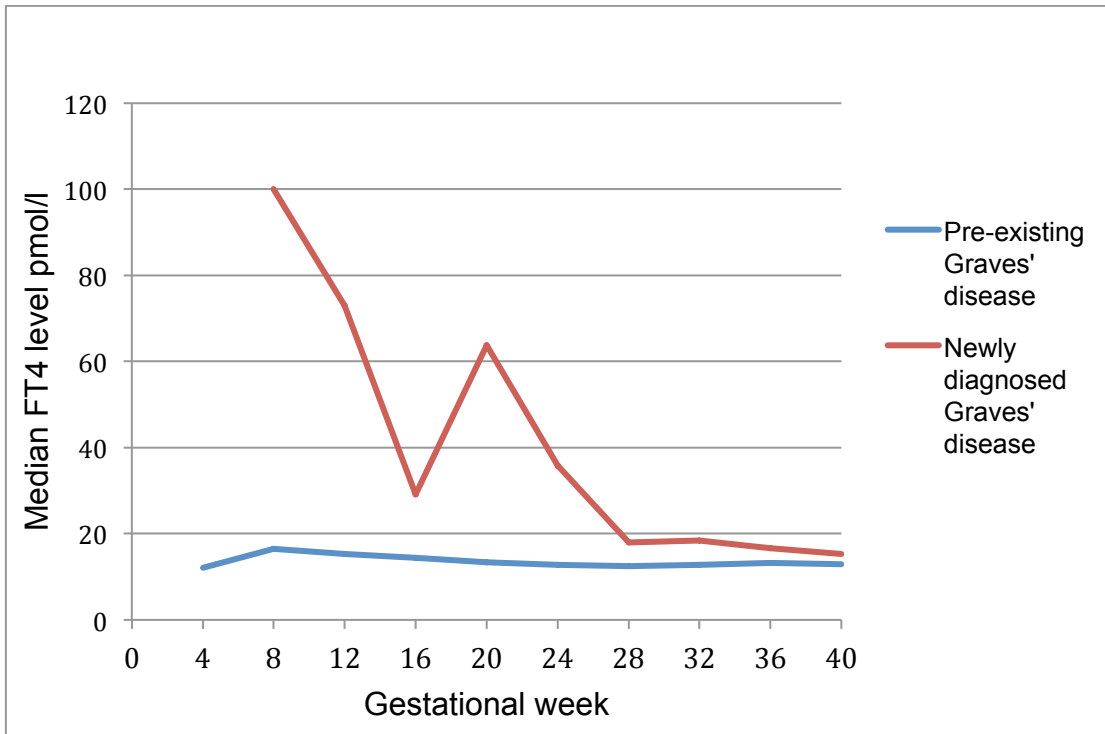


Figure 2: Median FT4 levels by week of pregnancy

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CHAPTER 3: APPENDICES

1.1 Data collection form

DATA COLLECTION FORM

Case Number: _____ Hospital No.: _____ Age: _____ Para: _____ Gravida: _____

On First Visit

Date Seen (year/month/day)	Pregnancy duration (weeks)	Weight (kg)	Diagnosis 1. Graves' disease 2. Graves' disease:hypothyroid post ¹³¹ I treatment 3. Thyrotoxicosis other 4. Hashimoto's disease 5. Hypothyroid post thyroidectomy 6. Euthyroid goitre 7. Congenital hypothyroidism	Date of Diagnosis (y/m/d)	Radioactive iodine 1. Yes 2. No	Date of ultrasound	Gestational age (GA) on fultrasound (U/S) (weeks)

Hyperthyroid patients			Measurements			Blood Investigations				Treatment	
Visits	Date (y/m/d)	GA (wks)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Weight (kg)	TSH (mIU/L)	ft4 (pmol/L)	ft3 (pmol/L)	Thyroid Antibodies 1. Yes 2. No	Drug 1. Carbimazole 2. Nil	Dose (mg)
1 st Visit											
2 nd Visit											
3 rd Visit											
4 th Visit											
6 th Visit											
7 th Visit											
8 th Visit											
9 th Visit											

Hypothyroid patients			Measurements			Blood Investigations				Treatment	
Visits	Date (y/m/d)	GA (wks)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Weight (kg)	TSH (mIU/L)	ft4 (pmol/L)	ft3 (pmol/L)	Thyroid Antibodies 1. Yes 2. No	Drug 1. Thyroxine 2. Nil	Dose (mg)
1 st Visit											
2 nd Visit											
3 rd Visit											
4 th Visit											
6 th Visit											
7 th Visit											
8 th Visit											
9 th Visit											

Delivery Detail

MATERNAL					
Date of Delivery (y/m/d)	Mode of Delivery 1. NVD 2. Caesarian Section 3. Awaiting delivery 4. Lost to follow- up	Maternal outcome 1. Delivered 2. Intrauterine foetal death 3. Spontaneous abortion 4. Molar pregnancy	Maternal Thyroid Function Test prior to delivery		
			TSH (mIU/L)	ft4 (pmol/L)	ft3 (pmol/L)

FOETAL								
Gender 1. Male 2. Female	Weight (kg)	Gestational Age (weeks)	Apgar 1. 1 minute 2. 5 minute	Foetal TFT			Age of baby (days)	Foetal anomalies 1. Thyroid disease/drug related 2. Other
				TSH (mIU/L)	ft4 (pmol/L)	ft3 (pmol/L)		

1.2 Ethics clearance



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Veronique Nicolaou

CLEARANCE CERTIFICATE

M120818

PROJECT

A Retrospective Analysis of Thyroid Disease
in Pregnancy at the Chris Hani Baragwanath
Academic Hospital, Soweto, South Africa

INVESTIGATORS

Dr Veronique Nicolaou

DEPARTMENT

Gestational Endocrine Clinic
Medical School

DATE CONSIDERED

31/08/2012

DECISION OF THE COMMITTEE*

Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 20/03/2015

CHAIRPERSON

A handwritten signature in black ink, appearing to read 'PE Cleaton-Jones'.

(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof R Shires

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES..