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ARTICLE

Prevalence and aetiology of thyrotoxicosis in patients with hyperemesis gravidarum presenting to a tertiary hospital in Cape Town, South Africa

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Background: The association between hyperemesis gravidarum (HG) and abnormal thyroid function is well known.
Aims: The prevalence, aetiology and course of thyrotoxicosis in women with hyperemesis gravidarum (HG) were studied.
Methods: Women admitted for HG, who underwent thyroid function evaluation between 1 August 2016 and 30 April 2019, were studied. Laboratory data included baseline human chorionic gonadotropin (hCG) and baseline (t1), discharge (t2) and follow-up (t3) thyroid function tests (thyroid stimulating hormone [TSH] and free thyroxin [fT4]). Available TSH receptor antibody status was assessed.
Results: Eighty-two patients were included. The incidence of thyrotoxicosis was 49% based on local laboratory TSH range and 48% if trimester-specific ranges used. In the majority of normal pregnancies, thyrotoxicosis was hCG-mediated (72.5%), 15% were confirmed to have Graves' disease and 12% had a molar pregnancy. Very high fT4 levels (> 40 pmol/l) at baseline [t1] were documented in 24% of women with hCG-mediated thyrotoxicosis. Clinical features were absent in a third of women with Graves' disease and the diagnosis was reliant on positive antibody status. Free T4 values declined from (t1) to later in gestation (t3) ($p < 0.001$).
Conclusion: The incidence of thyrotoxicosis in women with HG is high. Free-T4 values decrease with clinical stabilisation of HG, suggesting a contribution of dehydration to the large variation in baseline fT4 measurements. Testing for TSH-receptor antibodies should be considered in women with TSH < 0.01 pmol/l and persistent fT4 elevation on follow-up. Final review of thyroid function should be performed after 15 weeks' gestation.

Keywords: dehydration, Graves' disease, hCG-mediated thyrotoxicosis, hyperemesis gravidarum, thyrotoxicosis

Introduction

Nausea and vomiting in pregnancy have been documented throughout history. Medical literature cites Antoine Dubois, a consultant surgeon and a head obstetrician to Napoleon Bonaparte and his second wife Empress Marie Louise, as the first physician to describe the condition in 1852. Dubois described the syndrome as a 'pernicious vomiting of pregnancy' and the aetiology was unknown, but hypothesised to be due to 'irritation of the vomiting reflex from the stretching of the uterine fibres,' and 'irritation of the cervix'.[1] Since then, hyperemesis gravidarum has been increasingly recognised as an important cause of maternal and foetal morbidity and even mortality.

Hyperemesis gravidarum (HG) is intractable vomiting during pregnancy associated with dehydration, electrolyte and/or metabolic disturbances as well as weight loss of > 5% often resulting in severe ketonuria, haemoconcentration and electrolyte and liver enzyme derangements.[2] This condition represents the extreme of nausea and vomiting encountered during pregnancy and is reported to occur in only 0.1–0.2% of pregnancies, but remains a common reason for hospitalisation in the first half of pregnancy, second only to pre-term labour.[1,3] In South Africa the incidence of HG is uncertain; however, in-hospital maternal deaths attributable to HG have been reported.[4]

Human chorionic gonadotropin (hCG) is produced by placental trophoblasts and part of the glycoprotein hormone family, together with luteinising hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH). These hormones are heterodimers that share a common alpha-subunit and varying degrees of homology in their beta-subunits. There is considerable homology between the beta-subunits of hCG and TSH. As a result, hCG has weak thyroid-stimulating activity and may cause thyrotoxicosis during the period of highest serum hCG concentrations (peaks at 10–12 weeks' gestation). The range of hCG at peak is wide with values between 20 000–150 000 mIU/ml noted at the end of the first trimester. The thyroid stimulating effect of 1 mIU/ml of hCG is equivalent to 0.0013 mIU/l of TSH. Prolonged and significant elevation of hCG (usually more than 200 000 mIU/ml) is thus required to increase thyroid hormone production and cause clinical effects.[5]

Hyperemesis gravidarum is associated with higher levels of hCG and thus a potential cause of hCG-mediated thyrotoxicosis. It has also been proposed that the biological activity of the hCG found in patients with HG, specifically in terms of TSH receptor interaction, is enhanced.[6,7] Trophoblastic thyrotoxicosis and the rare entity of familial gestational thyrotoxicosis, due to a mutant TSH receptor that is hypersensitive for physiological hCG levels, represent the other forms of hCG-mediated thyrotoxicosis.

The transient thyrotoxicosis of HG must be distinguished from thyrotoxicosis of other non-pregnancy-related causes. In reproductive-aged females it is most likely Graves' disease. The

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presence of vomiting, the absence of goitre and ophthalmopathy, and the absence of a tachycardia greater than 100 beats/minute help to clinically differentiate. If Graves' disease is suspected, TSH-receptor antibodies should be tested and are positive in more than 90% of cases.[8] Furthermore, persistence of functional thyroid abnormalities beyond the first trimester of normal pregnancies is probably not hCG-mediated and also argues for exclusion of non-pregnancy-related causes such as Graves' disease.[9]

In view of the well-known association of HG with abnormal thyroid functions, many centres, including ours, routinely evaluate thyroid function as part of their work-up in women admitted for HG. Thyroid function is not done selectively based on a clinical concern of thyrotoxicosis. The thyroid abnormalities associated with HG are described in the literature as mild in nature and usually do not require therapy per se.[10,11]

Current treatment and management of HG includes resuscitation, identification and treatment of the cause of vomiting, correction of electrolyte imbalances, symptomatic support such as rehydration, anti-emetics, thiamine supplementation and nutritional as well as psychological support.[12]

With this study we sought to determine the prevalence and aetiology of thyrotoxicosis in women who presented with HG to Tygerberg Hospital's Obstetrics and Gynaecology Department over a time period of 44 months. The research will explore the contribution of a clinical evaluation to differentiate Graves' disease from the other aetiologies of thyrotoxicosis, will document the course of hCG-mediated thyroid dysfunction in the absence of thyroid pathology and evaluate the ideal timing of thyroid function testing in patients presenting with severe nausea and clinical dehydration in pregnancy. This may allow cost reduction in laboratory testing, shortened in-hospital stay and prevention of inappropriate thyroid-specific interventions.

Materials and methods

Design and study population

A descriptive study based on retrospective data collection was performed at Tygerberg Hospital (TH), affiliated to Stellenbosch University. All women who presented from August 2016 until April 2019 with HG or severe vomiting requiring admission to Tygerberg Hospital were considered for inclusion into the study. Patients were admitted for stabilisation and intravenous fluids and assessed by the responsible medical teams to have HG. It is standard practice in the Obstetrics Department of Tygerberg Hospital to routinely perform serum hCG and to do thyroid function testing on all patients with HG (TSH and fT4) on admission. Patients for whom baseline hCG measurements and thyroid function test results were not available were excluded from the analysis. Informed consent was waived due to the retrospective nature of data collection. The study complied with the World Medical Association Declaration of Helsinki and was approved and registered by the Human Research and Ethics Committee at the Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa (HEA-2018-8742).

Data collection

Patient clinical information and data were retrieved from the Tygerberg Electronic Content Management System (ECM) and biochemical results obtained via the National Health Laboratory System (NHLS) electronic platform. Strict confidentiality was maintained as the ECM and NHLS databases, as well as personal computers used for data collection, are password protected and therefore restrict access to data. Patient information and data were entered onto a spreadsheet using Excel version 2016 Microsoft Office Professional Plus (Microsoft Corp, Redmond, WA, USA). A unique number was linked to each patient's data set and the patient de-identified.

Demographics

Demographic data pertaining to maternal age, parity, gestational age at presentation, prior history or family history of thyroid disorders or hyperemesis gravidarum and human immunodeficiency virus (HIV) status if known were collected.

Biochemistry

Laboratory data collected included baseline hCG and thyroid function tests (TSH and fT4). Available data on follow-up thyroid function tests, at discharge and after 20 weeks of gestation, as well as TSH receptor antibody status, were also recorded.

Serum TSH, free T4 (fT4) and free T3 (fT3) in this study were measured on the Roche Cobas e 601 analyser (Roche Diagnostics, Mannheim, Germany). A competition principle immunoassay is used for the determination of free thyroxine fT4 and fT3 and results determined via a calibration curve. The measuring ranges for fT4 and fT3 are 0.3–100 pmol/l and 0.3–10 nmol/l and the normal reference intervals are 12–22 pmol/l and 3.1–6.8 nmol/l respectively. A non-competitive sandwich immunoassay is applied for TSH with the same principle as for fT3 and fT4. The TSH measuring range is 0.005–100 µIU/ml with a normal reference interval of 0.27–4.2 mIU/l. The local NHLS does not report trimester-specific normal ranges. The inter-assay coefficient of variance at various clinically significant cut-off points for serum TSH, fT4 and fT3 was less than 3%.

At baseline, a diagnosis of thyrotoxicosis was made in the presence of a suppressed TSH level based on the NHLS laboratory reference range and a concomitant increase in circulating levels of fT4 and/or fT3. Ideally TSH levels in pregnancy should be defined by population-based normative data in iodine-replete women. Globally the use of trimester-specific TSH ranges is advocated in in the absence of population-based reference data in view of the known lowering of both the lower and upper range of TSH, especially in the latter part of the first trimester (weeks 7–12). A TSH range of 0.1–2.5 mIU/l and a TSH range of 0.2–3 mIU/l are globally regarded as acceptable to apply for the first and second trimester of pregnancy in the absence of available population-based reference values.[11] Although we categorised patients as thyrotoxic or euthyroid based on the non-adjusted NHLS-TSH range, the impact of using trimester-specific TSH on the categorisation of women as thyrotoxic will be reflected on.

The iodine status of patients is not routinely assessed in this specific cohort and is a limitation of the current study.

TSH-receptor antibodies were measured using an electrochemiluminescence immunoassay (ECLIA) with the Cobas e immunoassay analysers. Results are determined via a calibration curve.[13] The normal reference interval in the NHLS laboratory is a value less than 1.00 U/l and a value above this is regarded as positive. Additional antibody testing was not done to confirm the underlying aetiology of thyrotoxicosis.

Serum from clotted blood was used for intact hCG measurement by means of a sandwich immunometric assay.

Statistical analysis

Statistical analysis was performed using GraphPad Prism (8.2.0) (https://www.graphpad.com/scientific-software/prism/). The normal distribution of data was determined using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Data are presented as either mean ± standard deviation (SD) (normal distribution) or median (interquartile range) (IQR) (non-parametric data). Student's t-test with two-tailed *p*-value and non-parametric Mann–Whitney tests were performed to determine differences between the thyrotoxic and euthyroid cohorts. The Kruskal–Wallis multiple comparisons test was used to determine differences between the hCG-mediated and Graves' diseases and molar pregnancy cohorts. Level of significance was accepted at $p < 0.05$.

Results

Demographic characteristics of the participants

The demographics of the total study cohort, the thyrotoxic cohort and the euthyroid cohort are summarised in Table 1.

Demographics and thyroid status of the total study cohort with HG

A total of 82 women with HG who underwent thyroid function testing were included in the study cohort. Almost half of women (40/82 [49%]) with HG were thyrotoxic at baseline. Seven women had suppressed but measurable TSH levels with normal circulating fT4 and fT3 in keeping with subclinical thyrotoxicosis. These women were classified within the euthyroid group and not regarded as having overt thyroid disease.

The mean age of the total study population was 26.4 ± 5.3 years and the age ranged between 16 and 41 years. Three-quarters (60/82 [73%]) were multigravidas, median gestation at presentation was 11 (IQR 8–14) weeks and the majority (54/82 [66%]) presented with HG in the first trimester of pregnancy. Only three women presented with HG after 18 weeks' gestation, two of whom had abnormal (molar) pregnancies. Multiple pregnancies were documented in only 4/82 (5%) and abnormal (molar) pregnancies were present in 9/82 (11%) women. The majority of women had testing for HIV (73/82 [95%]) – only 4/73 tested positive (5% of total study cohort).

Five women (5/82 [6%]) reported known prior thyroid disease. Clinical features of Graves' disease at presentation (presence of diffusely enlarged goitre with or without bruit and/or extra-thyroidal features including thyroid eye disease and/or pretibial myxoedema) was only present in four women; one of these women had known Graves' prior to the index pregnancy.

Demographics of the thyrotoxic and euthyroid study cohorts with HG

The demographic characteristics of the thyrotoxic (40/82) and euthyroid cohorts (42/82) were similar (Table 1). Similar age, ethnicity, parity, total number of first trimester presentations, pregnancy subtypes and HIV status were noted. Abnormal (molar) pregnancies occurred in both cohorts. Clinical features of Graves' disease were present in a small minority of women within the thyrotoxic group (4 [10%]).

Biochemical characteristics of the total study cohort with HG

Biochemistry at baseline in the women with and without thyrotoxicosis is depicted in Table 2. The median hCG level in the thyrotoxic cohort (195 431 mIU/ml [IQR134 733–334 871]) was significantly ($p < 0.001$) higher compared with the euthyroid

Table 1: Demographic characteristics of total, thyrotoxic and euthyroid cohorts with HG

Description	Total cohort ($n = 82$)	Thyrotoxic cohort ($n = 40$)	Euthyroid cohort ($n = 42$)
Age (years)[a]	26.4 ± 5.3	26.7 ± 5.4	26.0 ± 5.3
Ethnicity			
• Caucasian	3 (4%)	2 (5%)	1 (2%)
• Black African	30 (37%)	14 (35%)	16 (38%)
• Mixed ancestry	35 (43%)	17 (43%)	18 (43%)
• Unknown	14 (17%)	7 (18%)	7 (17%)
Gravidity			
• Primigravida	22 (27%)	11 (28%)	11 (26%)
• Multigravida	60 (73%)	29 (73%)	31 (74%)
• Miscarriage prior	23 (28%)	10 (25%)	13 (31%)
Gestation (weeks)[b]	11 (8–14)	12 (10–14)	10 (8–14)
• 1st trimester (1–12)	54 (66%)	25 (63%)	29 (69%)
• 2nd and 3rd trimester (13–40)	28 (34%)	15 (38%)	13 (31%)
Pregnancy subtype			
• Singleton	69 (84%)	33 (83%)	36 (86%)
• Multiple (Twins/triplets)	4 (5%)	2 (5%)	2 (5%)
• Molar	9 (11%)	5 (13%)	4 (10%)
Prior hyperemesis gravidarum	13/60* (%)	6/29* (21%)	7/31* (23%)
HIV status			
• Negative	68 (83%)	34 (85%)	34 (81%)
• Positive	4 (5%)	0 (0%)	4 (10%)
• Unknown	10 (12%)	6 (15%)	4 (10%)
Prior thyroid disease	5 (6%)	5 (13%)	0 (0%)
Clinical features of Graves' disease	4 (5%)	4 (10%)	n/a

Thyrotoxic cohort defined as patients with suppressed TSH according to local laboratory reference range in the presence of elevated circulating free T4 ± elevated free T3. Data expressed as *n* (%) except for age and duration of gestation which are expressed as mean ± SD[a] and median (25%–75% IQR)[b] respectively.*Denominator refers to multigravidas only. Statistical analysis: Student's t-test with two-tailed *p*-value[a] and non-parametric Mann–Whitney test[b]. No statistical differences were evident between the thyrotoxic and euthyroid cohorts.

Table 2: Biochemistry at baseline in the thyrotoxic and euthyroid cohorts with HG

Description	Thyrotoxic cohort ($n = 40$)	Euthyroid cohort ($n = 42$)
hCG on admission (mIU/ml)		
• Median[a]	195 431 (134 733–334 871)*	75 670 (33 652–193 688)*
• Highest value	2 194 200	622 485
• Lowest value	4459	4 447
Thyroid function tests		
TSH[a] (mIU/l):	0.01 (0.01–0.04)	0.86 (0.32–1.25)
• Suppressed value (0.01–0.26)	22 (55%)	n/a
• Unrecordable value (< 0.01)	18 (45%)	n/a
• Adjusted range[b]	39 (98%)	n/a
FT4[a] (pmol/l)	33.6 (25.1–45.1)	18.1 (15.2–21)
FT3[a] (nmol/l)($n = 15$)	12 (10.5–19)	5.2 (5.1–5.4)
TSH receptor antibody		
Measured	$n = 23$	n/a
Positive	5	n/a

Thyrotoxic cohort defined as patients with suppressed TSH according to local laboratory reference range and elevated circulating free T4 ± elevated free T3. Cohort size as noted in heading unless otherwise specified. Data are expressed as either n (%), absolute values or median (25%–75% IQR)[a]. Statistical analysis: non-parametric Mann–Whitney test [a]. *$p < 0.01$ indicates significant difference between the thyrotoxic and euthyroid cohorts. Adjusted range[b] refer to globally accepted trimester-specific TSH ranges (trimester 1: 0.1–2.5 mIU/l; trimester 2: 0.2–3.0 mIU/l). n/a = not applicable. Normal range fT4 = 12–22 pmol/l and normal range fT3 = 3.1–6.8 pmol/l.

group (75 670 mIU/ml [IQR33 652–193 688]), but with extreme ranges. A significant overlap is present between measured hCG levels in those with thyrotoxicosis (40/82) compared with euthyroid (42/82) women with no clear upper cut-off level to identify those at risk of elevated thyroid function (Figure 1).

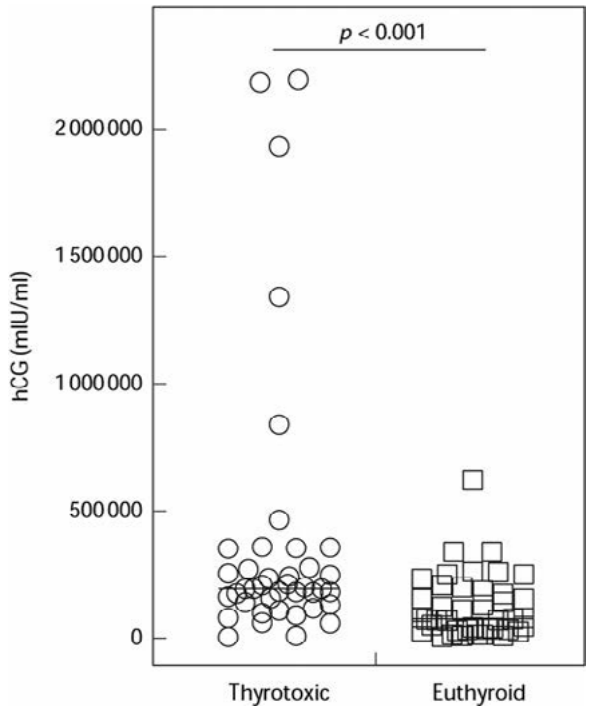

Figure 1: hCG at baseline in the women with and without thyrotoxicosis. Individual values are presented with the median indicated (solid line) for the thyrotoxic ($n = 40$) and euthyroid ($n = 42$) cohorts. Statistical analysis: Mann–Whitney test.

The median fT4 in the thyrotoxic cohort (40/82) was 33.6 pmol/l (IQR25.1–45.1), with the mean (39.2 pmol/l) near twice the upper limit of normal (ULN) of 22 pmol/l. Free T4 values at baseline ranged from 14.7 pmol/l to values 4.5x the ULN at 100 pmol/l, in 22/40 (55%) women with thyrotoxicosis fT4 values were more than 1.5 times the upper range of normal. The fT3 was performed in 15/40 women with thyrotoxicosis, with a median value of 12 nmol/L (IQR10.5–19) and the mean (15.5 nmol/l) more than twice the ULN for the local NHLS laboratory (6.8 nmol/l). In 10 of 15 women tested, the fT3 was more than 1.5 times the ULN.

The local NHLS laboratory report a normal TSH range irrespective of the duration of pregnancy. Application of globally accepted trimester-specific TSH ranges impacted minimally on classification of functional thyroid status in our cohort. In women with overt thyrotoxicosis, i.e. suppressed TSH values based on NHLS range and elevated circulating fT4, only one woman re-classified as being euthyroid based on a normal trimester-specific TSH. Three of the seven women with subclinical hyperthyroidism within the euthyroid cohort still fulfilled criteria for TSH suppression after correction based on trimester-specific TSH range. None of the women with HG had biochemical evidence of overt primary hypothyroidism.

Testing for TSH-receptor antibodies was performed in 23/40 (58%) women with a biochemical diagnosis of thyrotoxicosis and noted to be positive in 5/23 women. Antibody testing was performed in three of the four women who presented with clinical features suggestive of Graves' disease and was noted to be positive in all except one.

Biochemical characteristics in the thyrotoxic cohort within different aetiological subgroups

Graves' disease was confirmed to be the underlying aetiology in 6/40 women. Molar pregnancies were present in 5/40 of the thyrotoxic women and in 29/40 women the thyrotoxicosis was the result of hCG-mediated gestational thyrotoxicosis. The diagnosis of Graves' disease was based on clinical features and positive antibodies in three (3/6) women, clinical features only in one (1/6) woman and a positive antibody test in two (2/6) women in the absence of a clinical suspicion of Graves'. Molar pregnancy was the cause of the clinical presentation with HG in 9/82 women with associated thyrotoxicosis documented in 5/9 (56%).

The comparative baseline biochemistry of women with hCG-mediated thyrotoxicosis versus those with Graves' disease and underlying trophoblastic disease (molar pregnancy) is noted in Table 3. A significant difference in fT4 at diagnosis was only evident between women with hCG-mediated thyrotoxicosis and those with underlying molar pregnancies ($p = 0.036$). The extent of elevation of thyroid function tests in women with hCG-mediated thyrotoxicosis (29/40) varied significantly with the highest recordable fT4 value 100 pmol/l and the lowest value 14.7 pmol/l, the highest fT3 46.7 nmol/l and the lowest value 4.7 nmol/l (Table 3). In the 29/40 women, 12/29 women had a fT4 value elevated to more than 1.5x ULN of the laboratory and in 7/29 (24%) women the fT4 level exceeded 40 pmol/l. Likewise fT3 values ranged between a highest value of 46.7 nmol/l and lowest value of 4.7 nmol/l with values exceeding 1.5x ULN in 3/8 (38%) women in whom fT3 was assessed.

Table 3: Biochemistry at baseline in women with thyrotoxicosis ($n = 40$)

Description	hCG-mediated ($n = 29$)	Graves' disease ($n = 6$)	Molar pregnancy ($n = 5$)	p-*value*
hCG on Admission (mIU/ml)[a]				
• Median	194 282 (114 032–260 312)	187 327 (119 805–401 329)	1 931 600 (762 096–2 188 823)	0.017[#]
• Highest value	466 261	840 400	2 194 200	
• Lowest value	10 000	4 459	183 142	
Thyroid function tests[a]				
TSH (mIU/l):[a]				
• Suppressed value (0.01–0.26)	19 (66%)	0	3 (60%)	
• Unrecordable value (< 0.01)	10 (34%)	6 (100%)	2 (40%)	
• Adjusted range[b]	28 (97%)	6 (100%)	5 (100%)	
FT4 (pmol/l)[a]				
• Median	29.15 (23.63–38.70)	39.8 (38.08–46.90)	64.70 (40.55–70.70)	0.036[#]
• Highest value	100	52	72.3	
• Lowest value	14.7	35.9	27.2	
FT3 (nmol/l)[a]	($n = 8$)	($n = 5$)	($n = 4$)	n.s.
• Median	8.7 (6.2–18)	12.6 (11.9–17.7)	18.10 (12.0–28.8)	
• Highest value	46.7	19	31.8	
• Lowest value	4.7	11.7	10.5	

Cohort size as noted in heading unless otherwise specified. Data are expressed as either *n* (%), absolute values or median (25%–75% IQR)[a]. Statistical analysis: Kruskal–Wallis multiple comparisons test. [#]$p < 0.05$ indicates significant difference between the hCG-mediated ($n = 29$) and molar pregnancy cohorts ($n = 5$). No difference was evident between hCG-mediated vs. Graves' disease cohorts or the molar pregnancy vs. Graves' disease cohorts. Adjusted range[b] refers to globally accepted trimester-specific TSH ranges (trimester 1: 0.1–2.5 mIU/l; trimester 2: 0.2–3.0 mIU/l[b]; n.s. = not significant.). Normal range fT4 = 12–22 pmol/l and normal range fT3 = 3.1–6.8 pmol/l.

Course of hCG-mediated thyrotoxicosis in women with HG

The course of hCG-mediated thyrotoxicosis (29/40) was documented for the women with thyrotoxicosis at baseline who had follow-up assessment of fT4 prior to discharge (19/29) and later in gestation (13/29) as given in Table 4. The time interval from admission to discharge in these women ranged from two to seven days. Women were only treated for the HG and received no thyroid-specific therapy or intervention. Follow-up biochemistry in later gestation was recorded in 13/19 women with hCG-mediated thyrotoxicosis who also had thyroid function done at baseline and on discharge at a mean gestation of 17.4 ± 6 weeks. A significant spontaneous decline in fT4 values was observed from day of admission to a later stage in gestation ($p < 0.001$). Despite a decline already evident from admission to discharge, this did not reach significance ($p = 0.286$) (Figure 2A). A slight non-significant ($p = 0.056$) decline in fT3 values was also evident from day of admission to the later stage in pregnancy (Figure 2B).

Patients presenting with HG to Tygerberg Hospital, after resolution of the nausea and vomiting, are sent back to their respective primary or secondary referral centres for further management of the pregnancy. Available data pertaining to the pregnancy outcome in women with hCG-mediated thyrotoxicosis were limited and unknown in 17/29 women. Where birth data were available, live births were noted in 8/12 (67%) and a miscarriage/intrauterine death (IUDs) in four women with hCG-mediated thyrotoxicosis. In the women with normal thyroid function, birth data were unavailable in 18/41 women, 13 had live births (72%), four had either a miscarriage or IUD (22%) and one had a termination of pregnancy for unknown reason.

Discussion

In this study looking at thyroid status in women presenting with HG, nearly half of the cohort (49%) were thyrotoxic at baseline. In the vast majority of these women, the cause of thyrotoxicosis was hCG-mediated without any other cause present (72.5%). Graves' disease was identified as the underlying cause in six (15%) and an underlying molar pregnancy in five women (12.5%). Median fT4 levels were significantly higher in the thyrotoxic cohort with underlying molar pregnancy compared with the hCG-mediated subgroup only ($p = 0.035$), but a significant overlap in measured fT4 levels was, however, present amongst the different aetiological subgroups with no clear upper level fT4 able to distinguish any of the subgroups from one another. Extreme individual elevation in fT4 was also noted in women with hCG-mediated thyrotoxicosis; in seven women (24%) the fT4 value exceeded 40 pmol/l.

Table 4: Course of hCG-mediated thyrotoxicosis in women with HG on no thyroid treatment

Description	(t1) on admission	(t2) on discharge (2–7 days post admission)	(t3) later in gestation (mean 17.4 ± 6 weeks)	p-*value*
Thyroid function tests				
FT4 (pmol/l)[a]	*n = 19*	*n = 19*	*n = 13*	
• Median	32.1 (23.6–42.6)	26.7 (17.4–32)	15.25 (13.45–25.40)	[#]< 0.001
• Highest value	100	88.1	32.4	
• Lowest value	17.1	12.0		
FT3 (pmol/l)[a]	*n = 7*	*n = 7*	*n = 7*	
• Median	9.0 (6.2–20.4)	7.8 (4.6–9.3)	5.4 (4.2–6.5)	[#]0.056
• Highest value	46.7	10.1	7.0	
• Lowest value	4.9	4.2	4.2	

Data are expressed as either absolute values or median (25%–75% IQR)[a]. Statistical analysis: Kruskal–Wallis multiple comparisons test. [#]$p < 0.05$ indicates significant difference between values at admission and later in gestation.

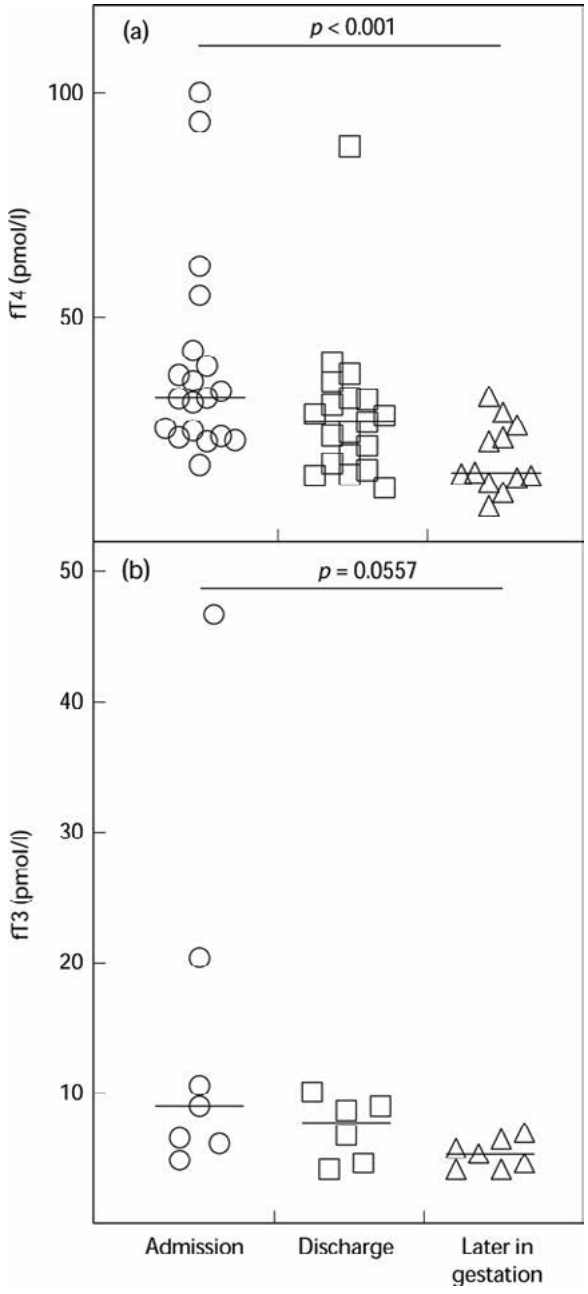

Figure 2: Course of hCG-mediated thyrotoxicosis in women with HG. Individual values are presented with the median indicated (solid line) for (A) fT4 and (B) fT3. Statistical analysis: Kruskal–Wallis multiple comparisons test. t1 = day of admission; t2 = day of discharge; t3 = later stage in gestation.

Hyperemesis gravidarum typically presents in the latter part of the first trimester, at a time when hCG, regarded as the main driver behind the extreme nausea and vomiting, is expected to be highest.[14] In addition, not only have higher circulating levels of intact hCG been noted, but it has also been reported that the form of hCG with increased affinity for the TSH receptor containing additional asialo-carbohydrate chains is increased in HG.[6, 7]

Our patients with HG and thyrotoxicosis presented at a median gestation of 12 weeks (IQR 10–14). The majority of the thyrotoxic cohort was represented by women with hCG-mediated TSH receptor stimulation with underlying normal pregnancies. The median hCG value noted in these women (Graves' and molar pregnancy excluded) was significantly higher than our euthyroid HG cohort and vastly exceeds the normal range for circulating intact hCG in the background population based on gestational age.[15,16] In a large prospective population-based cohort from the Netherlands ($n = 8\,065$ women), the normal reference range coinciding with the median gestation at presentation of our patients is 42 267 mIU/ml with a maximum recorded value of 144 054 mIU/ml; these values are markedly lower than the median hCG of 194 282 mIU/ml and maximum recorded value of 466 261 mIU/ml noted in our hCG-mediated thyrotoxic cohort and also lower than the median and maximum value observed in the euthyroid women.[15] We did not evaluate different isoforms or subtypes of hCG in our study cohort, but our work corroborates findings from other studies supporting the notion that the degree of elevated hCG determines the development of biochemical thyrotoxicosis in HG.[14, 17–19]

The prevalence of thyrotoxicosis in our cohort of women with HG was high, involved almost half of all women (49%) and in the majority was attributed to hCG-mediated thyrotoxicosis (72.7%). All women regarded as thyrotoxic had a suppressed TSH value based on the local laboratory non-pregnancy range and concomitant increased fT4 values. Ideally, population-based trimester-specific reference ranges for TSH should be used and defined through assessment of local population data in iodine-replete pregnant women.[20] It is recommended globally to use adjusted trimester-specific TSH ranges in the absence of locally available population data. Controversy remains as to exactly how to adjust given significant geographic and ethnic diversity, and also due to differences in laboratory methodology. Adjustment of TSH assessment based on globally accepted first and second trimester lower limits of normal, i.e. TSH values < 0.1 mIU/l and <0.2 mIU/l respectively, had very limited impact on categorisation in our patient cohort and resulted in a single patient re-categorised as euthyroid. The prevalence of thyrotoxicosis noted in our study is comparable to other published studies in the literature reporting that as many as 60% of women with HG exhibit thyrotoxicosis.[14,16] In a retrospective study looking at 143 women with HG, Sun *et al.*[21] reported an incidence of thyrotoxicosis in 48.3% of their cohort, a finding almost identical to ours. Similarly, the vast majority of thyrotoxic women had hCG-mediated thyrotoxicosis without underlying thyroid pathology (65/69; 95%). In a prospective observational study by Tan *et al.*, 53 of 87 women (61%) with HG presented with associated thyrotoxicosis and 44 were followed into later gestation. Only five patients in their cohort had underlying Graves' disease.[18]

In view of the well-known association between HG and thyrotoxicosis, it is standard practice in our institution to request evaluation of thyroid function on admission in all women with HG irrespective of the degree of TSH suppression. Testing for TSH-receptor antibodies is recommended in patients in whom the fT4 levels are elevated based on our NHLS laboratory range, but this recommendation is unfortunately not always adhered to. This is in line with the Endocrine Society Clinical Practice Guideline (2012) that recommends thyroid function and thyroid receptor antibodies be done in all patients with HG and biochemical evidence of thyrotoxicosis.[22]

The more recent updated guidelines from the American Thyroid Association (ATA) in 2017 recommend that fT4 should be done only if the TSH is suppressed < 0.1 mIU/ml, but do not propose

specific timing with regard to testing in women with HG. The updated guidelines also recommend TSH-receptor antibody testing only if the aetiology remains unclear after a careful clinical assessment.[20]

Interestingly, if clinicians abided by the 2017 updated recommendations of the ATA, all thyrotoxic patients with Graves' in whom a TSH value was available (5/6), 2 of the 5 women with molar pregnancy and 10 of the 29 women (34%) with hCG-mediated thyrotoxicosis qualified for fT4 testing. In the six women with hCG-mediated thyrotoxicosis in whom fT4 values were available at (t3), a TSH suppressed to below detectable limits (< 0.01 mIU/ml) did not signify unsuspected thyroid disease or the need for specific antithyroid therapy. Spontaneous resolution of elevated thyroid function without any thyroid intervention was noted in 5/6 women and fT4 remained only marginally elevated at 22.4 pmol/l (normal range up to 22 pmol/l) in one patient.

It is uncertain to what degree dehydration, with associated hypovolemia and haemoconcentration, at the time of admission in women with HG influences measures of both fT4 and fT3. Very little has been reported in the literature on this topic. In a single study, dehydration has been shown to profoundly affect total serum thyroid hormone concentrations due to changes in thyroid hormone-binding proteins, but also documented volume depletion to result in the elevation of free thyroxine. These elevations reverse acutely upon rehydration, in parallel with the decrease in extra-cellular fluid volume status markers.[16] In clinical practice, we have had similar experiences in that the abnormal thyroid biochemistry improves significantly and even normalises on adequate rehydration during hospitalisation. These high values may, in inexperienced hands, result in antithyroid therapy that may not be warranted and may not be in the patient's best interest.

Based on median fT4 values, a decline was observed in our patient group with hCG-mediated thyrotoxicosis from baseline (t1) to both later time points (t2 and t3), reaching significance only at (t3) ($p < 0.001$). With the exception of a single individual with a baseline minimal increase in fT4, a decline in fT4 was noted in all women from baseline to discharge (average time interval 2–5 days). The most overt decline, interestingly, was noted in those with extreme elevations (baseline >4 0 pmol/l) with an average decline of 26.7 pmol/l (range of decline 14.5–56.1 pmol/l). This raises the question as to the possible contribution of dehydration to measured values and the validity of measured free thyroid hormones at the time of volume depletion.

Few studies have been published in the literature looking at the course of hCG-mediated thyrotoxicosis into later gestation. Based on reported data, hCG-mediated thyrotoxicosis is expected to resolve at a time when circulating hCG-levels decline, i.e. from the 15th week of gestation onwards.[3,17,18] In a study by Sun and colleagues, a gradual decline in fT4 levels was noted one and two months after presentation with HG and thyrotoxicosis in all patients without any specific antithyroid intervention;[21] similarly Tan and co-workers documented normalisation in their thyrotoxic cohort in the middle of the second trimester without any antithyroid medication.[18] In our study a significant decline in fT4 was observed at (t3) from baseline assessment ($p < 0.001$); the timing of the follow-up assessment was, however, not standardised, but performed at a median of 17.4 weeks. In 8 of the 13 women in whom a follow-up fT4 was available, values normalised completely on follow-up, while in the remaining 5 slightly elevated fT4 was still present (none more than 1.5 times the upper limit of normal). In four of the five women with elevated fT4, the follow-up was done at 13–15 weeks' gestation – a time point earlier than noted for normalisation in other published work. The association between HG and thyrotoxicosis in other sub-Saharan populations has not been studied to date.

Although Graves' disease is responsible for the minority of cases with thyrotoxicosis in the setting of HG as noted in our study (6/40 [15%]) and in other published work (5/53 [9.4%]) in a study conducted by Tan *et al.*[18], and in 4/69 (5.8%) women in the study by Sun *et al.*[21], it is the commonest non-pregnancy related inherent thyroid condition responsible for thyrotoxicosis in reproductive-aged women and must not be overlooked. Graves' should be considered in any women with HG presenting with overt diffuse goitre (with or without an audible bruit), the presence of extra-thyroidal features such as thyroid orbitopathy or rarely with pretibial myxoedema and evidence of adrenergic overactivity, and can be confirmed with antibody testing. Care must, however, be taken not to over-interpret an appropriately increased pulse rate in the presence of significant dehydration. Tachycardia must thus be evaluated along with the rest of the patient's clinical presentation. Clinical features were not universally present in all women with Graves' disease in our study: in 2/6 (33.3%) of our Graves' cohort the diagnosis was based on antibody testing without clinical suspicion.

It has been suggested by some studies and even by the ATA that fT4 and especially fT3 is higher in women with Graves' disease compared with hCG-mediated thyrotoxicosis of HG, last mentioned as a result of the auto-immune process on the thyroid with increased intrathyroidal T3 production.[23] Higher hCG values have also been documented in those with hCG-mediated thyrotoxicosis compared with Graves' in women with HG.[17] This was not confirmed in our study at baseline assessment. There was a tendency for higher median fT4 and fT3 levels in the Graves' cohort, but these did not reach statistical significance. Interestingly, TSH values were noted to be unrecordable in all women with Graves' disease, but this was noted in only 34% of those with hCG-mediated thyrotoxicosis. This may indicate a longer period of sustained thyroid excess in women with Graves' and again raises the question as to the temporary effect of dehydration on measured thyroid hormone levels at the time of admission. Median hCG values were comparable in the two thyrotoxic groups.

The study had limitations. The retrospective nature of the study resulted in a lack of standardisation of treatment protocols and impacted on optimal timing and completeness of follow-up biochemistry. Trimester-specific TSH ranges were not used to define the thyrotoxic cohort and although the local TSH reference range correctly categorised 39 of the 40 thyrotoxic patients, future work in pregnancy should adhere to global recommendations. The study population was small and only 47.5% and 32.5% of the thyrotoxic cohort returned for follow-up assessment at (t2) and (t3) respectively. TSH receptor antibody testing was done in only half of the thyrotoxic women and could have been more easily regulated with a prospective study design.

Conclusion

Thyrotoxicosis is common in women presenting with HG and affects nearly half of all cases, with hCG-mediated thyrotoxicosis

the commonest aetiology. The fT4 values decreased with clinical stabilisation of HG, suggesting a possible contribution of dehydration to the large variation in baseline fT4 measurements noted. A future prospective study is, however, required to confirm this observation. Consideration should be given to postponing testing for thyroid overactivity until adequate rehydration has been ensured. The distinction between hCG-mediated thyrotoxicosis and Graves' disease is not always easy. A low threshold for TSH-receptor antibody testing should be maintained, especially in women with TSH < 0.01 mIU/l and in those with persistent fT4 elevation on discharge and later in gestation. Final review of thyroid function in women with HG should be standardised and ideally performed after 15 weeks' gestation.

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Supplementary material

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References

1. London V, Grube S, Sherer DM, et al. Hyperemesis gravidarum: a review of recent literature. Pharmacology. 2017;100:161–71. doi:10.1159/000477853.
2. Ayyavoo A, Derraik JGB, Hofman PL, et al. Hyperemesis gravidarum and long-term health of the offspring. Am J Obstet Gynecol. 2014;210(6):521–5. doi:10.1016/ j.ajog.2013.11.035.
3. Goldman AM, Mestman JH. Transient non-autoimmune thyrotoxicosis of early pregnancy. J Thyroid Res. 2011: 1–11. doi:10.4061/2011/142413.
4. Saving Mothers. 2017:Annual report on confidential enquiries into maternal death in South Africa. Dept of Health; 2017. p. 1–90. [Available at: www.health.gov.za]
5. Hershman JM. Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. Best Pract Res: Clin Endocrinol Metab. 2004;18(2):249–65. doi:10.1016/j.beem.2004.03.010.
6. Tsuruta E, Tada H, Tamaki H, et al. Pathogenic role of asialo human chorionic gonadotropin in gestational thyrotoxicosis. J Clin Endocrinol Metab. 1995;80:350–5. doi:10.1210/jcem.80.2.7852489.
7. Yamazaki K, Sato K, Shizume K, et al. Potent thyrotropic activity of human chorionic gonadotropin variants in terms of 125I incorporation and de novo synthesized thyroid hormone release in human thyroid follicles. J Clin Endocrinol Metab. 1995;80(2):473–9. doi:10.1210/jcem.80.2.7852507.
8. Davies TF, Roti E, Braverman LE, et al. Thyroid controversy-stimulating antibodies. J Clin Endocrinol Metab. 1998;83(11):3777–81. doi:10.1210/jcem.83.11.5056-1.
9. Moleti M, Di Mauro M, Sturniolo G, et al. Hyperthyroidism in the pregnant woman: maternal and fetal aspects. J Clin Transl Endocrinol. 2019;16:1–7. doi:10.1016/j,jcte.2019.100190.
10. Tingi E, Syed AA, Kyriacou A, et al. Benign thyroid disease in pregnancy: a state of the art review. J Clin Transl Endocrinol. 2016;6:37–49. doi:10.1016/j.jcte.2016.11.001.
11. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21:1081–125.
12. Ngene NC, Moodley J. Fatal encephalopathy complicating persistent vomiting in pregnancy: importance of clinical awareness on the part of healthcare professionals. South African Med J. 2016;106(8):792–4. doi:10.7196/SAMJ.2016.v106i8.10909.
13. Tozzoli R, Kodermaz G, Villalta D, Bagnasco M, Pesce G, Bizzaro N.. Accuracy of receptor-based methods for detection of thyrotropin-receptor autoantibodies: a new automated third-generation immunoassay shows higher analytical and clinical sensitivity for the differential diagnosis of hyperthyroidism. Auto Immun Highlights. 2010;1(2):95–100. doi:10.1007/s13317-010-0014-4.
14. Verberg MFG, Gillott DJ, Al-Fardan N, et al. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005;11:527–39.
15. Korevaar TIM, Steegers EAP, de Rijke YB, et al. Reference ranges and determinants of total hCG levels during pregnancy:the generation R study. Eur J Epidemiol. 2015;30(9):1057–66. doi:10.1007/s10654-015-0039-0.
16. Ybarra J, Fernandez S. Rapid and reversible alterations in thyroid function tests in dehydrated patients. Nurs Clin North Am. 2007;42(1):127–34. doi:10.1016/j.chur.
17. Goodwin TM, Montoro M, Mestman JH. Transient thyrotoxicosis and hyperemesis gravidarum: clinical aspects. Am J Obstet Gynecol. 1992;167(3):648–52. doi:10.1016/S0002-9378(11)91565-8.
18. Tan JYL, Loh KC, Yeo GSH, et al. Transient thyrotoxicosis of hyperemesis gravidarum. BJOG An Int J Obstet Gynaecol. 2002;109:683–8. doi:10.1111/j.1471-0528.2002.01223.x.
19. Goodwin TM, Montoro M, Mestman JH, et al. The role of chorionic gonadotropin in transient thyrotoxicosis of hyperemesis gravidarum. J Clin Endocrinol Metab. 1992;75(5):1333–7. doi:10.1210/jcem.75.5.1430095.
20. Alexander EK, Pearce EN, Brent GA, et al. Guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315–89. doi:10.1089/ thy.2016.0457.
21. Sun S, Qiu X, Zhou J. Clinical analysis of 65 cases of hyperemesis gravidarum with gestational transient thyrotoxicosis. J Obstet Gynaecol Res. 2014;40(6):1567–72. doi:10.1111/jog.12372.
22. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(8):2543–65. doi:10.1210/jc.2011-2803.
23. Ide A, Amino N, Kudo T, et al. Comparative frequency of four different types of pregnancy-associated thyrotoxicosis in a single thyroid centre. Thyroid Res. 2017;10(1):1–6. doi:10.1186/s13044-017-0039-0.

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