PREVALENCE OF GESTATIONAL THYROTOXICOSIS IN WOMEN WITH EMESIS DURING EARLY PREGNANCY AT KENYATTA NATIONAL HOSPITAL

BY

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A DISSERTATION PRESENTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF MEDICINE IN PATHOLOGY UNIVERSITY OF NAIROBI

DECLARATION

I certify that this dissertation is my original work and has not been presented for a degree in any other university

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LIST OF ABBREVIATIONS

β-HCG: Human chorionic gonadotrophin

GTT: Gestational Transient Thyrotoxicosis

PII: Plasma Inorganic Iodide

T3: Triiodothyronine

T4: Thyroxine

TSH: Thyroid Stimulating Hormone

FT4: Free Thyroxine

FT3: Free triiodothyronine

TG: Thyroglobulin

RAIU: Radioactive iodine uptake

BMR: Basal Metabolic Rate

O₂: Oxygen

TTR: Transthyretin

PTU: Propylthiouracil

IVF: Invitro fertilization

LH: Leutenizing Hormone

TBG: Thyroxine Binding Globulin

HEP-G2: Human epithelial cell line -2

SHBG: Sex Hormone Binding Globulin

KNH: Kenyatta National Hospital

ABSRACT

The study comprised of 72 pregnant women with emesis or hyperemesis gravidarum during the early pregnancy upto 16 weeks gestation. The main objective of the study was to determine the thyroid status of these women and to determine the prevalence of gestational transient thyrotoxicosis at Kenyatta National Hospital. The serum levels of FT3, FT4, TSH, and β-HCG were determined using the micro-particle enzyme immunoassay technique.

The prevalence of gestational transient thyrotoxicosis was found to be 8.3%.

Majority of the women studied were at a gestation of 8 to 11 weeks (38.9%). Fatigue was the commonest medical symptom among those studied (72.2%). A high proportion of the study subjects (63.9%) also reported weight loss or absence of weight gain during the current pregnancy.

Most of the patients studied (84.7%) had moderate vomiting (1 to 5 episodes of vomiting per day). Only 15.3% had more than five episodes of vomiting per day. There was a gradual increase in β-HCG to a peak at 12 – 15 weeks gestation followed by a decline.

Free T3 and FT4 levels in majority of the patients studied (90.3%) were within the normal range. Nineteen (26.4%) patients had low TSH levels and one patient (1.4%) had high TSH values.

There was a significant positive correlation between β-HCG levels and FT4/FT3 (P values < 0.05 respectively). There was a significant negative correlation between β-HCG and the TSH levels (p value < 0.05). The correlation between the severity of vomiting and the levels of FT3, FT4, TSH and β-HCG was not significant (p value > 0.05 for all).

INTRODUCTION AND LITERATURE REVIEW

Gestational transient thyrotoxicosis (GTT) is defined as a transient increase in thyroid secretion, of non-autoimmune origin, leading to thyrotoxicosis with highly variable degrees of severity, and occuring in women with an otherwise normal pregnancy, frequently in association with hyperemesis . GTT differs from Graves' disease in that it occurs in women without a past history of Graves' disease (31). It is estimated that 1-2 of every 1000 pregnancies is complicated by thyrotoxicosis (1).

The most common cause of hyperthyroidism in women of child-bearing age (both pregnant and non-pregnant women) is Graves' disease. In recent years, another cause has been characterized, that results from direct stimulatory effects of β-HCG on the thyroid. This can induce thyrotoxicosis transiently during the first half of gestation, and its prevalence is much higher than that of Graves' disease, although it has usually less severe clinical manifestations. The syndrome, referred to as gestational transient thyrotoxicosis (GTT), differs from Graves' disease in that it is not of autoimmune origin, and the course, fetal risks, and management and follow-up of both entities are different (2).

Numerous hormonal changes and metabolic demands occur during pregnancy, resulting in profound and complex effects on thyroid function. As thyroid diseases are, in general, much more prevalent in women during the childbearing period (than in men), thyroid disorders such as chronic thyroiditis, hypothyroidism and Graves' disease are relatively common in pregnant women.

New information regarding the relationships between pregnancy and the thyroid gland has clarified many aspects of the interactions between gestational processes and regulation of the thyroid system, both in normal individuals and patients with thyroid disorders.

THE THYROID PHYSIOLOGY

The thyroid gland produces all of the body's T4 (about 80- 90mcg/dl) but only 20% of body's T3 (about 8mcg). Eighty percent (80%) of T3 is produced by peripheral deiodination of outer ring of T4 (by type 1, 5' - deiodinase mainly in the liver and kidney little in the heart).

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Thyroglobulin (TG) is a glycoprotein involved in storage and synthesis of thyroid hormones. Most of it resides in the lumen of the follicles, which are lined by a single layer of cuboidal follicular epithelium. It is taken into follicular cells by endocytosis for synthesis of thyroid hormones. Parafollicular cells which secrete calcitonin do not border on the follicular lumen. Iodide(I) is trapped by thyroid cells (rate limiting step), iodide is then organified (oxidised to I, hypoiodous acid (HOI) or enzyme bound hypoiodite ([EOI]) and then bound to tyrosyl residues of thyroglobulin which forms mono-iodotyrosine(MIT) and di-iodotyrosine(DIT). When two (DIT) molecules fuse, thyroxine (T4,L-3,5,3',5'-Tetraiodothyronine is formed; When MIT and DIT are coupled, triiodothyronine (T3,L-3,3',5-triiodothyronine) is formed. Thyroid peroxidase, which is located on the apical side of the follicular epithelium, catalyzes organification and coupling. The newly formed hormones remain part of the thyroglobulin.

The ratio of T4 toT3 in thyroglobulin is 13:1. Thyroid hormome- thyroglobulin complex is absorbed into the vesicles. Thyroid hormones are released from thyroglobulin by proteolysis. All the steps above are controlled by thyroid stimulating hormone. Thyroid stimulating hormone secretion is controlled by thyrotrophin releasing hormone, plasma free T3 and T4 (negative feedback), and intrapituitary T4 toT3 conversion (T3 inhibiting TSH release). Thyroid hormones increase the basal metabolic rate of most cells and is required for bone growth and maturation of neurological tissue. Thyroid hormones are also required for normal lactation and is involved in fat, carbohydrate, protein and vitamin metabolism. T3 increases the cardiac out-put, contractility and heart rate and decreases systemic vascular resistance. Most (75%) of T4 is bound to thyroid binding globulin (TBG), with a small amount (15%) bound to thyroid binding prealbumin and to albumin (10%). Almost all (99.7%) of T3 is bound to TBG. 99.98% of T4 is bound. Free hormone is active. T3 is 3-5 times more potent than T4. T3 to TBG and T4 to albumin/TBPA are not tightly bound (as is T4 toTBG), so these hormones may be more available for tissue use. The half-life of T4 is 1 week while that of T3 is 1 day. Reverse T3 (3,3', 5- triiodothyronine) is formed from T4 (inner ring deiodination) by 5-deiodinase and is metabolically inactive (3).

MATERNAL THYROID PHYSIOLOGY

Numerous hormonal changes and metabolic demands occur during pregnancy, resulting in profound and complex effects on thyroid function.

Table I; Global regulation of the thyroid in normal pregnancy

Factors affecting Thyroid Physiology during normal Pregnancy	
Physiologic Change	**Thyroid related consequences**
Increased renal I- clearance	Increased 24-hr RAIU
Decreased plasma I- and placental I- transport to the fetus	In I- deficient women, decreased T4, increased TSH, and goiter formation
Increased O2 consumption by fetoplacental unit, gravid uterus and mother	Increased BMR
First-trimester increase in β-HCG	Increased free T4 and T3Decreased basal TSH (partial blunting of the pituitary-thyroid axis)
Increased serum TBG	Increased total T4 and T3
Increased plasma volume	Increased T4 and T3 pool size
Inner-ring deiodination of T4 and T3 by placenta	Accelerated rates of T4 and T3 degradation and production

Early in pregnancy there is an increase in renal blood flow and glomerular filtration which lead to an increase in iodide clearance from plasma (Table I). This results in a fall in plasma iodine concentrations and an increase in the iodide requirements from the diet (6).

In a collaborative study between the Universities of Massachusetts (USA) and Santiago (Chili), iodine metabolism was investigated in the 1st, 2nd, 3rd trimesters of gestation and again 1-10 months after delivery. Plasma inorganic iodide (PII) concentrations, urinary iodide levels (24-hr urine collections) and thyroid function (total T4 or FTI, TG, and TSH) were measured in 16 pregnant women. The results showed a wide variability in PII values (even within the same individuals) and in urinary iodide concentrations, but there was no trend for PII concentrations to be depressed during pregnancy. Mean iodine excretion ranged from 459 to 786 µg/day, respectively in postpartum and 3rd trimester. The authors concluded that in iodine-sufficient regions, pregnancy does not have a major influence on circulating iodine concentrations (7).

In regions where the iodine supply is borderline or low, the situation is different and significant changes occur during pregnancy (7). While 24-hr radioiodine uptake determinations are not performed in the pregnant state, past studies have shown this is increased (8).

There is a further increment in the iodine requirements, due to transplacental iodide transport necessary for iodothyronine synthesis by the fetal thyroid gland, which becomes progressively functional after the 1st trimester. The need for increased iodine requirements has been demonstrated in several studies that have documented that, when a pregnancy takes place in conditions with borderline iodine adequacy, significant increments in both the maternal and fetal thyroid volume occur, if no supplemental iodine is given during early pregnancy (9).

Effects of human chorionic gonadotropin on thyroid function

Recently, a study of desialylated and deglycosylated β-HCG, in an experimental setting using T3 secretion as the response parameter (in a serum-free culture system with human thyroid follicles), showed that the removal of the sialic acid or the carbohydrate residues from native β-HCG transformed such β-HCG variants into thyroid stimulating superagonists (11). Further evidence supporting a pathophysiological role of β-HCG to stimulate the human thyroid gland is found in studies of patients with hydatidiform mole and choriocarcinoma. In these conditions, clinical and biochemical manifestations of hyperthyroidism often occur and the abnormal stimulation of the thyroid is rapidly relieved after appropriate surgical treatment (4).

Hyperemesis gravidarum

Patients with hyperemesis gravidarum may have increases in free T4 and free T3 (12). This, together with the generalized illness associated with this syndrome, may make the differentiation of this transient thyrotoxic condition from Graves' disease difficult (13). Some studies indicated that in patients with hyperemesis, β-HCG may be higher than in unaffected women (14). This may be associated with an exaggerated stimulation of the thyroid, mainly in the 1st and also the 2nd trimester. This may extend to an elevation in serum free T3, despite the fact that these patients are often nutritionally compromised (by abundant vomiting) and one would expect to have a low T3 due to impairment of T4 to T3 conversion. As gestation proceeds and β-HCG levels fall, normal thyroid function is progressively resumed. In severe cases, antithyroid drug treatment may be required.

A recent study compared the charge-isoforms profiles of circulating β-HCG in pregnant women from different ethnic backgrounds (Samoan vs European) with hyperemesis gravidarum (HG)(16). The results confirmed an increase in total serum β-HCG concentrations as well as an increase in the proportion of acidic β-HCG variants in women suffering from HG, compared with matched control subjects. The same study also confirmed the association between the β-HCG concentrations reached in early pregnancy and the elevations in thyroid hormone levels. While there was no major association between HG and ethnic background, the authors observed a high prevalence of recurrent HG and a familial predisposition for this condition, suggesting that either long-term environmental factors or genetic factors may play a crucial role in the pathogenesis of HG and gestational transient thyrotoxicosis.

Changes in circulating thyroid hormone binding proteins

The increase in total serum T4 and T3 that occurs during pregnancy is due to an increase in serum thyroxine binding globulin (TBG) concentrations. Changes in TBG happen early and, by 16-20 weeks of gestation, TBG concentrations have doubled (2,7). The cause of the marked increase in serum TBG is probably multifactorial. Early studies showed that TBG biosynthesis was increased in primary cultures of hepatocytes from Rhesus monkeys, when primed with estradiol (17). However, the lack of increase of other binding proteins (such as CBG and SHBG) by estrogen in HEP-G2 cells

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raised the possibility that other factors might be operative in the pregnant state. Studies of the changes in the glycosylation patterns of TBG, induced by estrogen, have indicated that the increase in circulating levels of TBG was probably due in a large part to a reduction of its plasma clearance (18). There is a marked increase in the more heavily sialylated fractions of TBG in the sera of pregnant or estrogen-treated individuals. This increase in TBG's sialic acid content inhibits the uptake of the protein by specific asialylo-glycoprotein receptors on hepatocytes, and the more heavily sialylated proteins from pregnant sera have therefore a longer plasma half-life (19). Such alterations in sialylation are not found in TBG isolated from patients with congenital TBG elevation, the latter being due to a true over-production of the protein (20). Thus, in addition to the stimulatory estrogen effects of estrogen on TBG synthesis, a major contribution to the increased TBG concentration during pregnancy is the reduced clearance of the protein. This explanation would also account for the increases observed in concentrations of other circulating glycoproteins in hyperestrogenemic states. Delivery leads to a rapid reversal of this process and serum TBG concentrations return to normal within 4-6 weeks. Serum T4 and T3 also return to pregestational serum levels. In addition to the 2 to 3-fold increase in serum TBG, modest decreases in both serum transthyretin (TTR) and albumin are commonly found in pregnancy, but the physiological impact of these changes, if any, is unknown (21).

Increased plasma volume

The increased plasma concentration of TBG, together with the increased plasma volume, results in a several-fold increase in the total T4 pool during pregnancy. While the changes in TBG are most dramatic during the first trimester, the increase in plasma volume continues until the time of delivery. Thus, for the free T4 concentration to remain unaltered, T4 production rate must increase (or its degradation rate decrease) to allow for the additional T4 to accumulate. The evidence that L-thyroxine requirements are markedly enhanced during pregnancy in hypothyroid treated women strongly suggests that not only T4 degradation is decreased in early pregnancy but also that an increased T4 production must occur throughout gestation, for maintaining the homeostasis of free T4 concentrations (22).

Thyroxine production rate

The only direct measurements of T4 turnover rates in pregnancy were obtained more than 30 years ago by Dowling et al (23). In eight pregnant subjects (4 in the 1st half and 4 in the 2nd half of gestation), T4 turnover rates were estimated not to be significantly different from those of non-pregnant subjects. However, based on considerations from more recent work ,T4 production rates are enhanced during pregnancy. Good evidence supporting these conclusions has arisen from the analysis of L-thyroxine administration in pregnant women with hypothyroidism. In 9/12 women with primary hypothyroidism who received stable L-thyroxine doses, there was a significant increase in serum TSH during gestation, requiring an compensatory increase in thyroxine dosage to restore euthyroidism (24). In this study, the few patients who did not require an increase in L-thyroxine dosage were receiving slightly excessive replacement doses prior to gestation. If the increased levothyroxine dose was maintained into the postpartum period, there was a subsequent increase in free T4 and a decrease in TSH . These results showed that there was an increase in T4 requirements, beginning already in early gestation, and which persisted until delivery. In another study, L-thyroxine replacement was evaluated in two groups of hypothyroid patients during pregnancy; one group had Hashimoto's disease while the second had had thyroid ablation for either Graves' disease or thyroid carcinoma (25). While the patients with thyroid ablation (because no residual tissue was present) required a 45% increase in L-thyroxine dosage to maintain euthyroidism during gestation, only a 25% increase was necessary in those with Hashimoto's disease (because some functional thyroid tissue was still present). From the point-of-view of maternal thyroid function during pregnancy, it is now accepted that there is a 30-50% increase in T4 production during gestation (5).

Placental metabolism of thyroid hormones

The placenta contains high concentrations of the Type 3 or inner-ring (5) iodothyronine deiodinase (26). The inner-ring deiodination of T4 catalyzed by this enzyme is the source of high concentrations of reverse T3 present in the amniotic fluid. Reverse T3 levels parallel maternal serum T4 concentrations (27). This enzyme may function to reduce the concentration of T3 and T4 in the fetal circulation (the latter being still contributed by 20-30 % from thyroid hormones of maternal origin at the time of parturition), although fetal tissue T3 levels can reach adult levels due to the action of the

ype 2 deiodinase (22). The Type 3 deiodinase may also indirectly provide a source of iodide to the

etus via iodothyronine deiodination. However, despite the presence of placental Type 3 deiodinase in

ircumstances in which fetal T4 production is reduced or maternal free T4 markedly increased,

ransplacental passage occurs and fetal serum T4 levels are about one third of normal (28). Thyroxine

s also detectable in amniotic fluid prior to the onset of fetal thyroid function (29).

THYROTOXICOSIS

The causes of thyrotoxicosis include those that are evident in the general population, as well as others

that occur only during pregnancy. Clinical entities such as toxic adenoma, multinodular toxic goiter,

subacute or silent thyroiditis, iodide-induced thyrotoxicosis, and thyrotoxicosis factitia are extremely

uncommon during pregnancy. Molar disease should always be considered and can potentially lead to

severe thyrotoxicosis (particularly in pregnant women with a pre-existing autonomous or nodular

goiter). However, uncomplicated hydatidiform mole is now easily diagnosed in the early stages of

gestation, and therefore rarely leads to severe thyrotoxicosis (4). Other extremely rare causes include

hyperplacentosis and struma ovarii (5).

Diagnosis of thyrotoxicosis in pregnancy

The clinical diagnosis of thyrotoxicosis in the pregnant woman may be difficult because of the

similarity between hyperdynamic symptoms and signs frequently observed in euthyroid pregnant

women and in thyrotoxicosis.

GESTATIONAL TRANSIENT THYROTOXICOSIS

GTT differs from Graves' disease in that it occurs in women without a past history of Graves' disease

and in the absence of detectable TSH receptor antibodies. GTT is not always clinically apparent,

since it is most often transient. Its etiology is directly related to the thyrotropic stimulation of the

thyroid gland associated with β-HCG (31).

Owing to its transient nature, the clinical manifestations of the disorder are not always apparent or

routinely detected. Hyperemesis is frequently associated with the most severely thyrotoxic cases, and

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in some women the symptoms are sufficiently alarming to require hospitalization for treatment. In most cases, no specific treatment is required and the symptoms can be relieved by the administration of beta-adrenergic blocking agents for a short period (less than 2 months). In some cases, the severity of the clinical presentation may require treatment with PTU, usually for a few weeks. By coincidence, GTT may occur in women with preexisting thyroid disorders, such as glandular autonomy, autoimmune thyroiditis or cryptic Graves' disease, and even in women with resistance to thyroid hormone (34). The association of GTT with an underlying thyroid abnormality often leads to more severe presentations of thyrotoxicosis, and β-HCG stimulatory action may presumably help to explain the rare cases of exacerbation of thyrotoxicosis due to Graves' disease that are infrequently encountered during the 1st trimester. Finally, when women with GTT were followed during a subsequent pregnancy, the syndrome has a characteristic tendency to reappear.

Twin pregnancy and GTT

Twin pregnancy is a naturally occurring clinical condition associated with sustained and high β-HCG concentrations. A group of women with a twin pregnancy was investigated prospectively during early gestation for the occurrence of GTT; the gestational age was known precisely since conception had been obtained by IVF. The study group was compared with singleton pregnancies, also obtained after IVF.

The results of the study showed that peak β-HCG values were significantly higher (almost double) and of much longer duration in twin pregnancy. While peak β-HCG values >75,000 U/L lasted less than a week in singleton pregnancies, peak β-HCG levels >100,000 U/L (and often reaching 200,000 U/L) lasted for up to 6 weeks in some of the twin pregnancies. Twin pregnancy was associated with a more profound and frequent (3-fold) blunting in serum TSH. Also, while free T4 concentrations remained unaltered in singleton pregnancy, they often rose transiently above normal in twin pregnancy. Symptoms related to thyrotoxicosis were usually absent or mild, except for emesis, which was more frequently noted.

Pathogenic mechanisms of GTT

Increased circulating β-HCG levels

The precise pathogenic mechanisms underlying GTT are still not fully understood. It remains possible that abnormal molecular variants of β-HCG, with a prolonged half life, are produced in these situations explaining sustained high circulating β-HCG levels, or β-HCG variants with a more potent thyrotropic activity (36). It has also been hypothesized that a dysregulation of β-HCG production may transiently take place (34). Based on the example of GTT in twin pregnancy, a quantitative direct effect of elevated β-HCG to stimulate the thyroid gland may presumably be sufficient to explain GTT in most pregnant women, provided that β-HCG values remain above 75,000-100,000 U/L for a sufficient period of time. GTT is directly related to both the amplitude and duration of peak β-HCG. Whatever the final explanation, the effects of β-HCG to stimulate the thyroid gland can best be explained by the marked homology that exists between the β-HCG and TSH molecules, as well as between the LH/CG and TSH receptors (37,39). Thus, GTT can be considered an example of an endocrine " spill-over " syndrome, a concept based on the molecular mimicry between hormone ligands and their receptors (31,39,40).

Hypersensitive TSH receptor mutations

An unresolved question is whether the thyroid gland is the passive bystander (or the victim) of abnormal thyrotropic activity of β-HCG in GTT, or whether the gland itself, through variable degrees of sensitivity of the TSH receptor, may play an active role in its responsiveness to the action of β-HCG. So far, only one example has been reported with a substantially increased sensitivity of the TSH receptor to the stimulatory effect of β-HCG, due to a single mutation in the extracellular domain of the TSH receptor (K183R) (41). The mutant TSH receptor was more sensitive than the wild-type receptor to β-HCG, thus accounting for recurrent thyrotoxicosis during pregnancy in the presence of normal β-HCG levels. This finding raises the possibility that some women who develop GTT may have an abnormality at the level of the thyroid follicular cell. In further studies of structure-phenotype relationship at the level of the TSH receptor, Vassart & Costagliola carried out site-directed mutagenesis, substituting lysine 183 in the ectodomain of the TSH receptor by a variety of amino

acids expressing different physicochemical properties (42,43). Unexpected results were obtained, since all TSH receptor mutants displayed a widening of their specificity toward β-HCG stimulation. Modeling of the mutated receptors indicated that the increased gain of sensitivity might result from the release of a nearby glutamate residue (in position E157) from a salt bridge formed with K183. As of now, this situation remains exceptional since most cases with GTT do not seem to be familial and they almost invariably have β-HCG levels >100.000 U/L (44).

Hyperemesis gravidarum and GTT

GTT is often associated with nausea (morning sickness), increased vomiting and hyperemesis gravidarum, a severe condition requiring hospitalization and drastic treatment (45). Studies have now established the correlation between severity of emesis and frequent abnormalities of thyroid function.

In a case report by Jeffcoate et al (43), a Pakistani woman who had hyperemesis gravidarum in each of her first two pregnancies was found to be biochemically thyrotoxic on each occasion. She was 26 years when she presented with vomiting, lassitude and weightloss during the 9th week of her first pregnancy. She was withdrawn, wasted and apathetic with tachycardia although no specific clinical signs of thyroid disease.Treatment with carbimazole (10mg twice daily) was commenced at 15 weeks and was accompanied by prompt improvement in her sickness and malaise. In February 1983 she presented at 11 weeks of pregnancy again with hyperemesis. Treatment with carbimazole 5mg three times daily was started at 13 weeks and was followed by a marked clinical improvement.

They concluded that: -

Some women with true hyperemesis gravidarum may have occult thyrotoxicosis and that this may result from stimulation of the thyroid grand by β-HCG.

Occult thyrotoxicosis may cause the gastrointestinal upset and treatment with carbimazole should be considered especially if the diagnosis of true hyperemesis gravidarum is made early (43).

RATIONALE OF THE STUDY

In spite of the recognition of some association between gestational transient thyrotoxicosis and hyperemesis gravidarum important questions regarding the presentation and management of hyperthyroidism in GTT and hyperemesis gravidarum are unresolved.

Bouillon et al studied 30 patients aged 15 to 42 years (mean age 26 years) admitted to the department of obstetrics of the University Hospital of Leuven because of hyperemesis gravidarum. An increased free thyroxine (T4) was observed in 73% of 30 consecutive pregnancies complicated by severe hyperemesis gravidarum. A low birth weight was observed in children born to hyperthyroxinemic mothers. The authors recommended further studies to evaluate more clearly the thyroid status of these patients and to seek a therapy which improves the birthweight of their childen (44).

Gestational transient thyrotoxicosisis is a common condition among pregnant women in the first ½ of gestation.Its prevalence is much higher than that of Graves' disease, although it has usually less severe clinical manifestations. As previously discussed, some studies from Europe indicated that the prevalence of GTT might represent 2-3 % of all pregnancies which is ten times more than Graves' disease (32). There is no local study which has been carried out to establish the prevalence of this condition in our setting despite the fact that many pregnant women present with symptomatology consistent with this syndrome e.g. weight loss or the absence of weight increase, tachycardia, unexplained fatigue and vomiting during the first half of gestation. In some women the symptoms are sufficiently alarming to require hospitalization for treatment. Thyroid profiles are rarely done if at all on these patients and in most cases symptomatic treatment is done with anti-emetics and intravenous fluids at Kenyatta National Hospital.

If the prevalence of gestational trasient thyrotoxicosis is established to be significant in this study, it will enable proper diagnosis to be made in future so that patients with this condition can be managed adequately. When women with GTT were followed during a subsequent pregnancy, the syndrome has a characteristic tendency to reappear and this necessitates that proper diagnosis is made right from the beginning.

Hyperthyroidism probably occurs more frequently during pregnancy than usually believed. It may be considered that perhaps up to 3% of all pregnancies may be complicated by some form of thyroid over-function. This justifies for systematic screening of pregnant women for hyperthyroidism.

Last but not least, a better understanding of the complex maternal-fetal inter-relationships related to the ongoing thyroid processes must remain our constant quest.

OBJECTIVES OF THE STUDY

BROAD OBJECTIVES

To determine the thyroid status of pregnant women with emesis upto 16 weeks gestation in Kenyatta National Hospital.

To determine the prevalence of gestational thyrotoxicosis among patients with emesis during early pregnancy.

SPECIFIC OBJECTIVES

1. To estimate serum levels of FT4, FT3, TSH and β-HCG in women presenting with emesis during early pregnancy at Kenyatta National Hospital.
2. To correlate serum levels of β-HCG with the serum levels of TSH, FT3 and FT4.
3. To correlate serum levels of β-HCG, FT3, FT4 and TSH with the severity of vomiting.
4. To make recommendations on the need to evaluate thyroid status in patients with emesis based on the study findings.

RESEARCH QUESTIONS

1. What is the prevalence of thyrotoxicosis in women with emesis during early pregnancy?

2. Does the serum β-HCG level correlate with the presence of thyrotoxicosis in emetic patients in early pregnancy?

3. What is the thyroid status of patients with emesis in early pregnancy?

4. Is the severity of vomiting correlated with serum β-HCG or thyroid hormone levels?

5. Is there need to estimate thyroid hormone levels in patients with emesis during early pregnancy?

MATERIALS AND METHODS

STUDY DESIGN

This was a descriptive cross – sectional study.

STUDY AREA

The study area was Kenyatta National Hospital acute gynaecology ward and the ante-natal clinic. Clients attending ante-natal clinic for the first time were registered on Monday morning and were then allocated to the various firms to be seen in the rest of the weekdays. About 50 to 70 new clients were registered every Monday in the ante-natal clinic. In the acute gynaecology ward, acute gynaecological cases such as hyperemesis gravidarum and abortions were admitted for management. About 2-3 cases of hyperemesis gravidarum were admitted every week in the acute gynaecology ward during the study period.

The National public laboratory was used for the determination of serum TSH, β-HCG, FT3 and FT4 levels.

STUDY DURATION

The study was conducted within a duration of six months between August 2004 and February 2005.

THE STUDY POPULATION

The study population consisted of patients with emesis during the early pregnancy seen in the ante-natal clinic and those admitted with hyperemesis gravidarum in the acute gynaecology ward.

CASE DEFINITION

Hyperemesis gravidarum was defined as intractible vomiting with dehydration occurring upto 16 weeks gestation in the absence of other signs and symptoms suggestive of any other illnesses.

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Emesis was defined as vomiting occurring upto 16 weeks gestation in the absence of other signs and symptoms suggestive of other illnesses.

INCLUSION CRITERIA

1. All patients admitted with hyperemesis gravidarum in the acute gynaecology ward who gave consent to participate in the study.

2. Patients seen in the ante-natal clinic with amesis during the early pregnancy (upto 16 weeks gestation) who gave consent to participate in the study.

EXCLUSION CRITERIA

1. All patients who were known to have had thyroid disorders before pregnancy. This was elicited through history and physical examination.

2. All patients with early pregnancy emesis but had other signs and symptoms suggestive of other illnesses.

SAMPLE SIZE

The sample size was 72 subjects calculated from a prevalence of 5% obtained from Asian study where the prevalence varied from 0.3%-11% (31). The level of precision was 0.05.

SAMPLING METHOD

All consecutive patients seen in the ante-natal clinic with emesis or admitted with hyperemesis gravidarum were approached to enter into the study.

RECRUITMENT

The principal investigator identified the suitable clients. He attended the ante-natal clinic every Monday morning when new clients were being registered to identify cases, fill the questionnaire and then collect specimens from the recruited patients.

The investigator liased with the registrars rotating in the acute gynaecology ward to identify cases admitted with hyperemesis gravidarum.

DATA COLLECTION

(a) Consent

The consent for participation was sought from the patients selected for participation in the study. This was done by the principal investigator at the acute gynaecology ward and the ante-natal clinic.

(b) Administration of the Questionnaire

The administration of the questionnaire (appendix I) was done after the consent had been obtained, history taken and physical examination done by the principal investigator. This was done by directly interviewing the participants of the study. Further information was obtained from the patients file notes.

(c) History and physical examination

History was taken to solicit for;

-   Symptoms of thyroid dysfuctions.
-   Gestational period. Where history and physical examination could not confirm pregnancy, a pregnancy test was done to confirm this.
-   Past medical history and drug therapy eg operations on the thyroid gland, use of anti- thyroid drugs and radiotherapy.
-   History of vomiting during this pregnancy.
-   General physical examination to check for tachycardia, hypertension, tachypnoea and fever was done.
-   Examination of the thyroid gland was done to rule-out the presence of a goitre.

(d) Specimen collection, transport and storage

Sample collection was performed, after acquisition of the consent. This was done in the antenatal clinic and in the acute gynaecology ward. Specimen collection was done using evacuated containers. Four millimeters of whole blood was collected in plain containers. The specimens were transported to the laboratory soon after collection. Serum was prepared and the specimens were stored at $-70°C$ until the time for analysis.

(e) Specimen analysis

Laboratory tests for serum TSH, FT3, FT4 and β-HCG were run using the Abbott IMX machine which uses microparticle enzyme immunoassay technology (MEIA) (appendix III). The tests were run at the National Public Health Laboratory . The tests were run together after the sample collection was complete. For the determination of β-HCG level the serum was diluted in the ratio of 1:400 so that the absolute level of β-HCG could be obtained. Before running the tests for each of the parameters, the machine was calibrated with six calibrators which were supplied with the standard kits by the manufacturer. The standard curves were established and used to determine the test values.

The results were recorded in the table of results (appendix IV).

(f) Quality Assurance

Three control samples low, medium and high were included in each run for the tests. The control samples were supplied together with the kits by the manufacturer. Acceptable internal quality control was taken as a control value within ± 2 standard deviations of the mean value provided by the kit manufacturer.

Data analysis

The data from the laboratory investigation results and the questionnaire was fed into a coded proforma sheets that was entered onto a computer database. Computer generated spreadsheets was prepared from the database and then transferred to SPSS® statistical software for analysis. β-HCG

levels were transformed to logs due to the large figures involved and the large variation in the figures. Pearson's correlation was used for test of significance.

ETHICAL ISSUES

1. Authority was sought from the Kenyatta National Hospital ethical and research committee.

2. The study was undertaken after formal approval by the committee (appendix V).

3. Informed consent was obtained from the participating subjects (appendix II).

4. Confidentiality of the participating subjects was maintained. The name of the subjects appeared on the questionnaire only for the purpose of follow-up when necessary.

5. The results of the tests done were communicated to the attending obstetrician for timely and continued management of the involved subjects and those to be seen in the future.

RESULTS

The study was conducted between July 2004 and December 2004. A total of 72 women with emesis during early pregnancy were studied. Their ages ranged from fourteen to thirty eight years with an average of twenty-five years (Table II). The majority of the women were in the age group 24 – 28 years. The parity ranged from 0+0 to 4+4.

Table II; Age distribution of the patients with emesis during pregnancy (n=72)

Age (years)	Number	Percentage
14 - 18	4	5.6
19 -23	26	36.1
24 – 28	27	37.5
29 – 33	11	15.3
34 - 38	4	5.6
Total	72	100.0

Table III; Gestation period of the patients with emesis during pregnancy (n=72)

Gestation(weeks)	Number	Percentage
4 - 7	7	9.7
8 - 11	28	38.9
12 - 15	21	29.2
16	16	22.2
Total	72	100.0

The gestation period ranged from four weeks to sixteen weeks with a mean of 11.46 weeks. Majority of the women studied were at a gestation of 8 to 11 weeks (38.9%) (Table III).

Symptoms	Frequency	Percentage
Fatigue	52	72.2
Weight loss or absence of weight gain	46	63.9
Palpitations	34	47.2
Backache	3	9.7
Abdominal pain	11	35.5
Dizziness	6	19.4
Others	8	25.8

Fatigue was the commonest medical symptom among those studied (72.2%). A high proportion of the study subjects (63.9%) reported weight loss or absence of weight gain during the current pregnancy (Table IV).

Six (8.3%) of those studied were currently on medications. 33.3% were on pain killers with the rest being on ventolin, buscopan, antacids and pregnidoxine.

Figure I: Severity of vomiting among the patients with emesis (n=72)

How many times are you vomiting per day?
■ 1 - 5 times
■ 6 - 10 times
□ 11 - 15 times
■ 16 - 20 times

1.39%
12.5%
84.72%
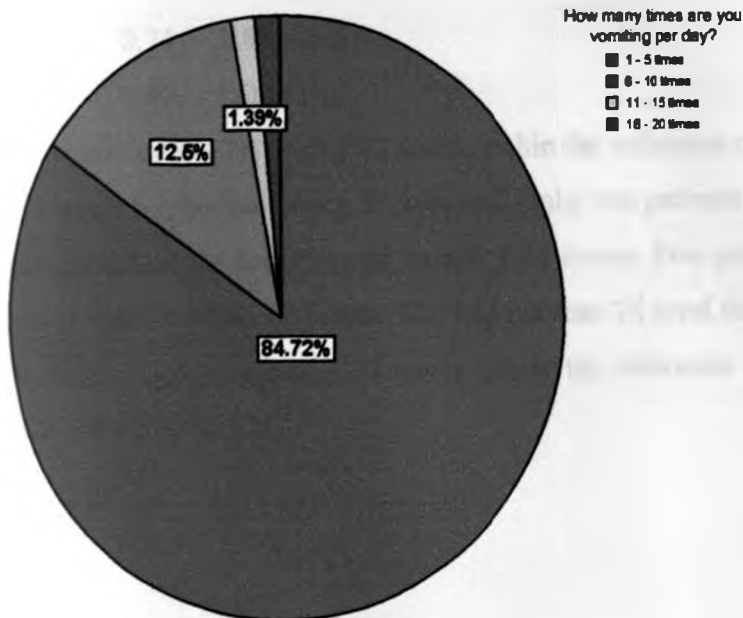
Most of the patients (84.7%) had moderate vomiting (1 to 5 episodes of vomiting per day). Only 15.3% had more than five episodes of vomiting per day (fig I).

Table V: Thyroid hormone levels in patients with emesis during pregnancy (n=72)

Hormone Levels	Number	%	Mean	Std Dev	Range
FT3 (pg/ml)					
Low	2	2.8	1.23	0.55	0.78
Normal	65	90.3	2.35	0.34	1.51
High	5	6.9	13.25	10.72	23.50
FT4 (ng/dl)					
Low	2	2.8	0.52	0.24	0.68
Normal	65	90.3	1.03	0.27	1.07
High	5	6.9	4.06	1.76	3.65
TSH (µiu/ml)					
Low	19	26.4	0.21	0.15	0.44
Normal	52	72.2	1.80	1.16	4.37
High	1	1.4	5.31	-	-

The reference ranges used for FT3, FT4 and TSH levels are (54,55);

FT3   1.68 - 3.54 pg/ml

FT4   0.71 - 1.85 ng/dl

TSH   0.47 - 5.0 µiu/ml

Most patients (90.3%) had FT3 levels within the reference range. Five (6.9%) of the patients had high FT3 levels the highest being 27.24pg/ml. Only two patients (2.8%) had low FT3 levels.

Again most of the patients had normal FT4 levels. Five patients (6.9%) had a high FT4 levels. Two patients had low free T4 levels. The highest free T4 level observed was 6.00ng/dl.

19 patients (26.4%) had TSH levels below the reference range. Only one patient (1.4%) had high TSH value (Table V).

TSH level	Low FT4	Normal FT4	High FT4	Total
Low TSH		14(19.4%)	5(6.9%)	19(26.4%)
Normal TSH	2(2.8%)	50(69.4%)		52(72.2%)
High TSH		1(1.4%)		1(1.4%)
Total	2(2.8%)	65(90.3%)	5(6.9%)	72(100%)

here were five patients with high FT4 and low TSH levels. Fourteen (19.4%) of those with normal T4 levels had low TSH levels. Both patients with low FT4 had normal TSH values while the one atient with a high TSH value had a normal FT4 value (Table VI).

TSH	Low FT3	Normal FT3	High FT3	Total
Low TSH	1(1.4%)	13(18.1%)	5(6.9%)	19(26.4%)
Normal TSH	1(1.4%)	51(70.8%)		52(72.2%)
High TSH		1(1.4%)		1(1.4%)

five patients (6.9%) with high FT3 had low TSH level. One patient had both low TSH and low levels. One patient had normal TSH and low FT3 level. Again one patient had high TSH level and ormal FT3 level.

r of the patients (5.6%) had both high FT3 and FT4 with a corresponding low TSH levels.

Figure II: β-HCG levels in relation to the gestation of the women studied
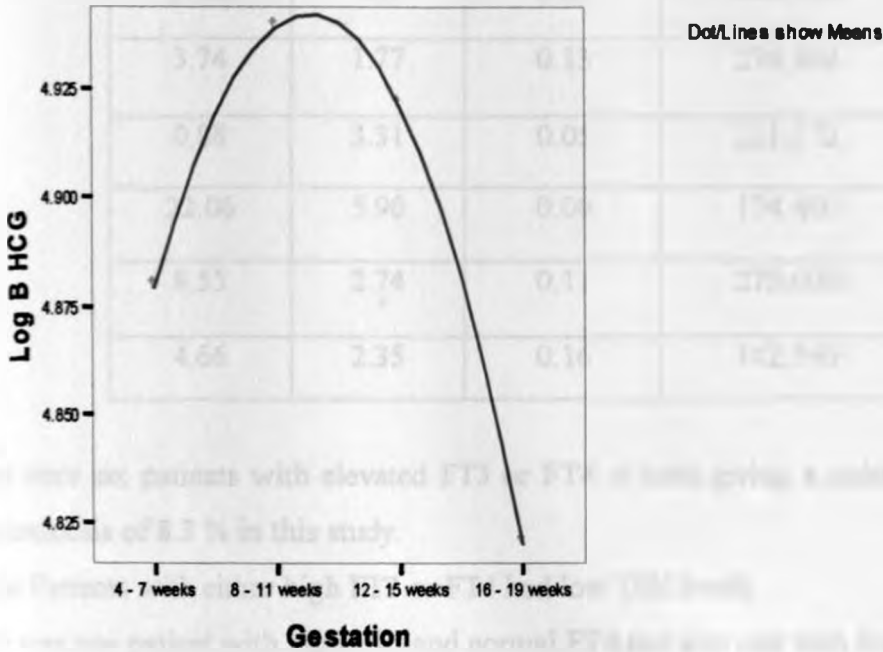
The β-HCG level among the 72 study subjects ranged from 1,664 miu/ml to 286,628 miu/ml with a mean of 121,740 miu/ml. There was a gradual increase in β-HCG to a peak at 12 – 15 weeks gestation (mean 283,136 miu/ml) followed by a decline (figure II).

The reference ranges of β-HCG in relation to the gestation are (51,52);

Gestation (weeks)	β-HCG (miu)
3 - 4 weeks	9 - 130
4 – 5 weeks	75 – 2,600
5 – 6 weeks	850 – 20,800
6 – 7 weeks	4,000 – 100,200
7 – 12 weeks	11,500 – 290,000
12 – 16 weeks	18,300 – 137,000

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FT3(pg/ml)	FT4(ng/dl)	TSH(µiu/ml)	β-HCG (miu/ml)	Gestation (Weeks)
27.24	6.0	0.01	268,188	10
3.74	1.77	0.13	274,808	8
0.88	3.31	0.05	221,172	11
22.06	5.90	0.00	174,400	13
8.55	2.74	0.11	279,600	16
4.66	2.35	0.16	142,560	9

There were six patients with elevated FT3 or FT4 or both giving a point prevalence of gestational thyrotoxicosis of 8.3 % in this study.

All the Patients with either high FT3 or FT4 had low TSH levels.

There was one patient with high FT3 and normal FT4 and also one with low FT3 and high FT4.

All those with high FT3 or FT4 values had β-HCG levels above the mean value for the study subjects and also on the higher side of the reference ranges (Table VIII).
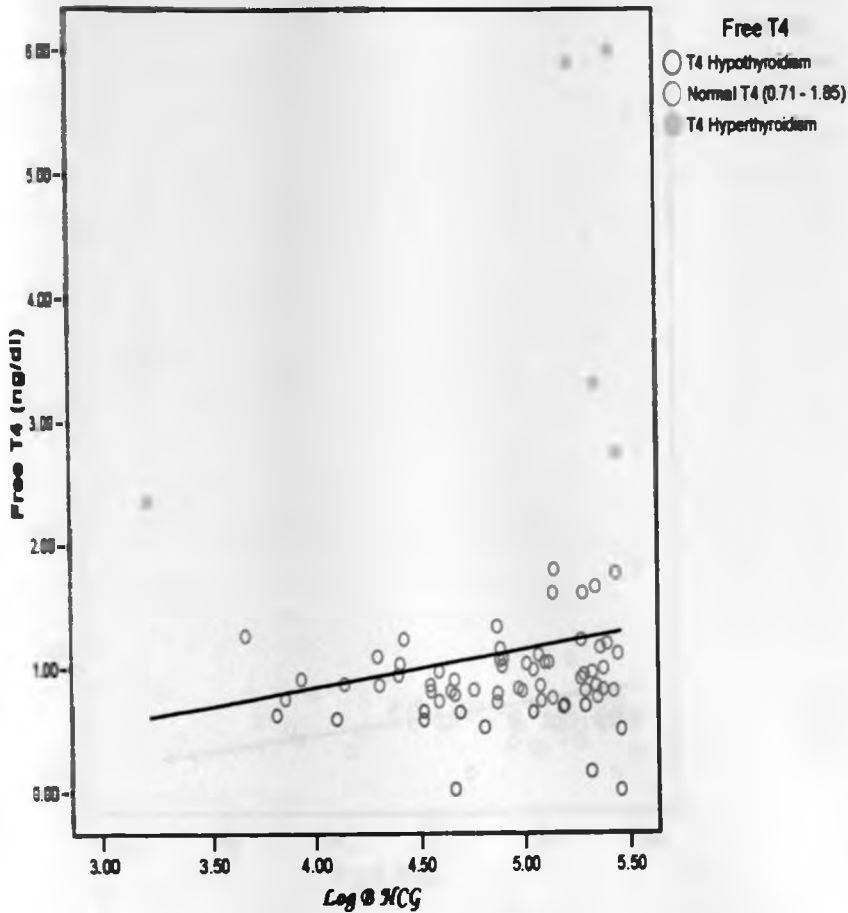
There was a significant positive correlation between β-HCG levels and FT4 levels with a P value of 0.025. Those with high FT4 had corresponding higher levels of β-HCG compared to those with either low or normal FT4 (figure III).
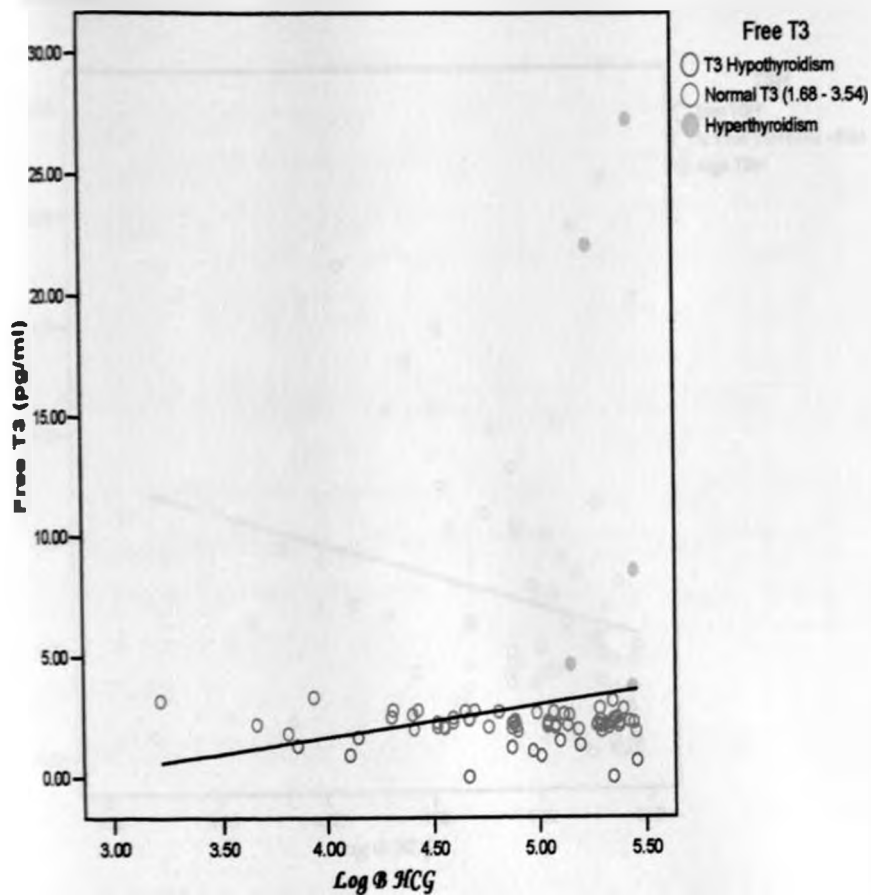
There was a significant positive correlation between β-HCG levels and FT3 levels with a P value of 0.023 (figure IV)
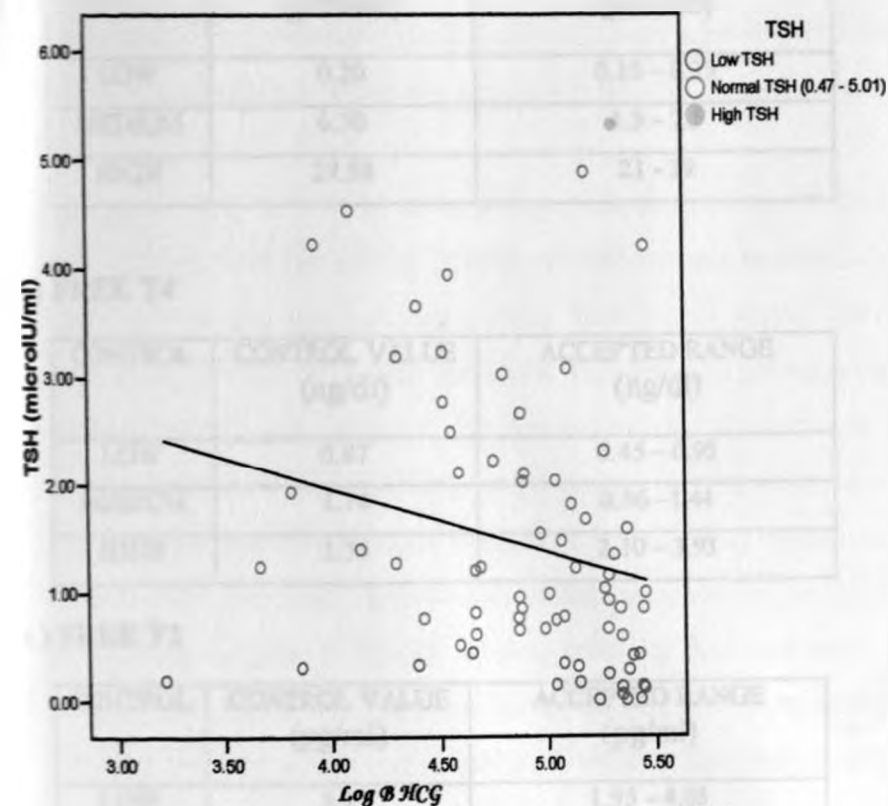
There was an inverse relationship between TSH and β-HCG levels.

There was a significant negative correlation between β-HCG and the TSH levels

(p value < 0.05) (figure V).

The correlation between the severity of vomiting and the levels of FT3 was not significant (p value = 0.659).

The correlation between the severity of vomiting and the levels of FT4 was not significant (p value = 0.615).

The correlation between the severity of vomiting and the levels of β-HCG and TSH was not significant (p value = 0.750 and 0.465 respectively).

a) TSH

CONTROL	CONTROL VALUE (μIU/ml)	ACCEPTED. RANGE (μIU/ml)
LOW	0.20	0.15 – 0.35
MEDIUM	6.30	4.5 – 7.5
HIGH	29.58	21 - 39

(b) FREE T4

CONTROL	CONTROL VALUE (ng/dl)	ACCEPTED RANGE (ng/dl)
LOW	0.87	0.45 – 0.95
MEDIUM	1.74	0.96 –1.44
HIGH	3.56	2.10 – 3.93

(c) FREE T3

CONTROL	CONTROL VALUE (pg/ml)	ACCEPTED RANGE (pg/ml)
LOW	3.1	1.95 – 4.05
MEDIUM	5.7	4.50 – 7.50
HIGH	11.4	8.0 – 16.00

(d) β-HCG

CONTROL	CONTROL VALUE (mIU/ml)	ACCEPTED RANGE (mIU/ml)
LOW	24.4	20 - 30
MEDIUM	149.8	120 - 180
HIGH	746	600 - 900

Three control samples low, medium and high were included in the tests for TSH, FT3, FT4 and β-HCG (Table IX). The control samples were supplied together with the kits by the manufacturer.

DISCUSSION

The study group comprised of 72 pregnant women upto a gestation of 16 completed weeks . The mean age of those studied was 25 years and their ages ranged from 14 to 38 years. Only 4 (5.6%) of those studied were within the age-group 34 – 38 years the rest being below this age.

This age distribution in the study group could be attributed to trends in the attendance of the ante-natal clinic where the young women are encouraged to attend the ante-natal clinic immediately they discover that they have conceived. Multigravid women are likely to delay in the attendance of ante-natal clinic upto late gestation. Furthermore primigravidas are more likely to seek for medical attention in cases of any complications of pregnancy than multigravidas who might assume symptoms like vomiting to be normal in pregnancy. Studies in Kenya have shown that higher parity women are more likely than lower parity women to see no one for ante-natal care. Only slightly over half (52%) of all women make four or more ante-natal visits in Kenya. Overall the median number of months of pregnancy at first ante-natal visit is 5.9 months (56). Other studies have shown that women who are most likely to have emesis or hyperemesis gravidarum during pregnancy are younger than those without this complication during pregnancy. A matched study of 58 pregnant Chinese women showed that women with hyperemesis gravidarum were younger than those without the complication (46).

The mean parity of those studied was 1 + 0. This low mean parity is in keeping with the young age of the study subjects where 57 (79.2%) of study group was less than 30 years of age.

The prevalence of gestational thyrotoxicosis in this study was found to be 8.3 %. Gestational thyrotoxicosis was defined as the presence of an elevated FT4 or FT3 or both with a corresponding depressed level of TSH in a patient with emesis during pregnancy.
This prevalence of gestational thyrotoxicosis in this study corresponds with other studies done in other regions of the world where the prevalence of gestational thyrotoxicosis was found to vary from 0.3% in Japan to 11% in Hong Kong (31).

Prospective studies from Europe have indicated that the prevalence of gestational thyrotoxicosis is 2-3 % (10-fold more prevalent than Graves' disease during pregnancy) (32). This is slightly below what was observed in this study where the prevalence was 8.3 %.

Cases followed-up for a few weeks after parturition showed that gestational transient thyrotoxicosis was always transient and serum free T4 normalized in parallel with the decrease in β-HCG concentrations (32).

There were discordances between TSH and the free thyroid hormones in this study the most common being low TSH with normal FT3 and FT4 which was found in fourteen (19.4 %) patients. The possible explanations to this are sub-clinical thyrotoxicosis or resolving thyrotoxicosis. Subclinical thyrotoxicosis is defined as a low serum thyrotrophin (TSH) concentration in a patient with normal serum free thyroxine (FT4) and triiodothyronine (FT3) concentrations. The secretion of TSH may be suppressed even in the presence of normal serum thyroid hormone levels. This reflects the highly sensitive response that the pituitary gland mounts to minor changes in serum FT4 and FT3 concentrations (48).

Another possible explanation could be the suppressive effects of β-HCG on the TSH production during pregnancy.

Studies have revealed that despite the cases of obvious thyrotoxicosis where the TSH level is low with elevated levels of FT3 and FT4, in some cases the serum TSH may remain partially suppressed for several weeks after the FT4 and FT3 have reverted to normal in patients who had gestational thyrotoxicosis previously (33,34,35).

Other studies showed that the serum TSH might be transiently suppressed in 10-20% of euthyroid women at the time of peak β-HCG levels (33).

Three patients had either low FT3 or FT4 levels with normal TSH values. These could possibly be cases of euthyroid sick syndrome where systemic non thyroidal diseases affect the free thyroid hormones. In this study all the patients had emesis some of them severe emesis (15.3%) and this could have had effects on the thyroid hormones. Euthyroid sick syndrome can be described as abnormal findings on thyroid function tests that occur in the setting of a non thyroidal illness without preexisting hypothalamic-pituitary and thyroid gland dysfunction. After recovery from

non thyroidal illness, these thyroid function test result abnormalities should be completely reversible.

Multiple alterations in serum thyroid function test findings have been recognized in patients with a wide variety of non thyroidal illness without evidence of preexisting thyroid or hypothalamic-pituitary disease. The most prominent alterations are low serum triiodothyronine (FT3) and elevated reverse T3 (rT3). Thyroxine (FT4), and free T4 index (FTI) also are affected in variable degrees based on the severity and duration of the non thyroidal illness. As the severity of the non thyroidal illness increases, both serum T3 and T4 levels drop and gradually normalize as the patient recovers (47)

Two patients with high TSH levels had normal FT3 and FT4 levels. This could probably be cases of early primary hypothyroidism. Hypothyroidism occurs during pregnancy relatively frequently. A nation-wide US survey showed that 4.6% of the population 12 years old and older had hypothyroidism and that 4.3% of all women suffered from thyroid disease or were taking thyroid medication. Routine prenatal screening showed that 2.2% of pregnant women in their second trimester had thyroid-stimulating hormone (TSH) levels at or above 6 µIU/L. The most common cause of primary hypothyroidism in women of reproductive age is chronic autoimmune thyroiditis, unless there is iodine deficiency or hypothyroidism that results from previous radical treatment for hyperthyroidism using radioiodine or surgery. Pregnant patients with hypothyroidism are at increased risk of obstetric complications, such as fetal death, gestational hypertension, placental abruption, and poor perinatal outcome (49, 50,).

There was one patient who had low TSH with low free thyroid hormones. Despite the fact that this was considered to be a case of secondary hypothyroidism further evaluation of the other anterior pituitary hormones needs to be done to confirm pituitary gland pathology.

In this study the level of β-HCG was highest at 12 – 15 weeks gestation where the mean level was 283,136miu/ml. The lowest level was at 4 – 7 weeks gestation where the mean was 99,750miu/ml. This gestation at which the peak β-HCG level occurred was slightly higher than what other workers had shown (51,52).

Human chorionic gonadotropin (β-HCG) is a peptide hormone composed of two subunits termed the alpha and beta chains. The alpha subunit is identical to that of TSH, while the beta chains differ between both molecules. The partial structural homology between β-HCG and TSH provides an indication that β-HCG may act as a "thyrotropic" hormone, by overlap of their natural functions. It has been established that β-HCG does possess an intrinsic (albeit weak) thyroid-stimulating activity and perhaps even a direct thyroid-growth-promoting activity. β-HCG stimulate the thyroid gland to increase the production of thyroid hormones and through the negative feedback mechanism production of the TSH from the anterior pituitary gland is suppressed (10).

Studies have shown that the level of human chorionic gonadotrophin is highest at the gestation of 7 – 12 weeks where the expected reference range is 11,500 – 289,000 miu/ml. Gestational thyrotoxicosis result from direct stimulatory effect of human chorionic gonadotrophin on the thyroid gland therefore inducing thyrotoxicosis transiently during the first half of gestation (7).

Those with high FT4 levels had a mean β-HCG level of 189,004 miu/ml with those having low FT4 having a mean β-HCG level of 116,729 miu/ml.

Those with high FT3 had a mean β-HCG level of 227,911 miu/ml compared to those who had low FT3 levels where the mean β-HCG level was 103,638 miu/ml.

Other studies have also indicated that in patients with hyperemesis during pregnancy, β-HCG may be higher than in unaffected women. This may be associated with an exaggerated stimulation of the thyroid mainly in the 1st and also the 2nd trimester (14).

In this study a significant positive correlation was found between β-HCG and FT4/FT3 levels (P values 0.025 and 0.023 for FT4 and FT3 respectively).

A significant negative correlation between TSH and β-HCG levels was found (p value 0.025).

These findings are similar to those of Yeo et al (53) who investigated the prevalence of gestational thyrotoxicosis in Asian women in Singapore and and found-out that the total and free β-HCG correlated negatively with TSH (P < 0.0001 and P < 0.0001, respectively), positively with FT4 (P < 0.001 and P < 0.001) and FT3 (P < 0.001 and P < 0.01) (53).

Similarly the positive correlation between the thyroid hormones and the β-HCG levels during pregnancy in this study corresponds with other studies which have shown that normal women may develop gestational transient thyrotoxicosis when they have abnormally elevated peak β-HCG levels and when these are sustained during an unusually prolonged period (35,37).

Of the women studied, 61 (84.7%) had 1 – 5 vomiting episodes per day. Only 11 (15.3%) reported more than five vomiting episodes per day.

Gestational transient thyrotoxicosis has now been associated with nausea (morning sickness), increased vomiting and hyperemesis gravidarum (45). Several studies have indicated a correlation between severity of emesis and frequent abnormalities of thyroid function (31,33,40). A common observation among obstetricians is that women with a twin pregnancy often experience severe vomiting during early gestation. Since there is no indication of increased vomiting among pregnant women with Graves' disease, hyperemesis in pregnancy appears to be associated mainly with β-HCG induced thyrotoxicosis. A possible explanation is that elevated and sustained β-HCG levels in the circulation promote estradiol production in these women: the combination of high β-HCG, estradiol and free T4 concentrations, by some yet not fully understood mechanism, transiently promotes emesis near the period of peak β-HCG (31,33,40).

Kimura et al (31) examined thyroid function and symptoms of thyrotoxicosis in relation to emesis in normal pregnancy. Thyroid function was evaluated in view of the clinical thyrotoxic symptoms and the severity of gestational emesis in early pregnancy of 51 normal women who were divided into three groups: those without emesis (n = 24), with emesis (n = 19) and with hyperemesis (n = 8). Serum free T4 and free T3 were higher in the hyperemesis group (P < 0.01) and the emesis group (P < 0.01), and serum TSH was suppressed to less than 0.1 µIU/ml in both groups, while serum β-HCG was not significantly different among these three groups. They concluded that Clinical thyrotoxicosis is caused by circulating β-HCG with higher biological activity in pregnant women with hyperemesis (31).

In another case control study, women with hyperemesis gravidarum were shown to be younger and had higher free T3 and T4 levels, as well as higher β-HCG level. The determinant for hyperemesis

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in the stepwise logistic regression analysis of the data, showed that the principal causal factor was the high free T4 levels, and not the high β-HCG levels. Thus, these results reinforce the notion that β-HCG causes hyperemesis gravidarum, by stimulating the thyroid gland to induce gestational transient thyrotoxicosis (46).

Some reports have indicated that up to two thirds of pregnant women presenting with hyperemesis have biochemical features suggesting hyperthyroidism (with an increased free T4 and suppressed TSH) and that the more seriously ill among these women also have an elevation in serum free T3 (15). Some investigators showed that the severity of emesis correlated with the levels of free T4 and β-HCG' (and TSH suppression), suggesting strongly that hyperemesis reflects the extreme of the spectrum of the physiological changes that occur in normal pregnancy (13).

Murphy et al (15) studied sixty seven patients seen at Los Angeles County Women's Hospital over a 10 month period with hyperemesis gravidarum with respect to thyroid function. Forty four patients (66%) had biochemical hyperthyroidism or suppressed thyroid stimulating hormone that was self limiting, resolving by 18 weeks gestation. The severity of hyperemesis was found to vary directly with the degree of hyperthyroidism (15).

In this study however, there was no significant correlation between the severity of vomiting and the levels of FT3 , FT4 , TSH and β-HCG. This lack of correlation may be explained by the fact that only a few of those studied (15.3%) had hyperemesis gravidarum the rest having relatively mild emesis during pregnancy.

Among the study subjects, 72.2% presented with fatigue, weight loss or absence of weight gain during the current pregnancy (63.9%) and palpitations (47.2%). Other symptoms included abdominal pain (35.5%) and dizziness (19.4%). In this study all the patients with elevated levels of both FT4 and FT3 presented with unexplained fatigue and also complained of palpitations. Two of them complained of absence of weight gain during the current pregnancy.

The historical clues and physical findings in pregnant patients with gestational thyrotoxicosis have been found to be similar to those occurring in non-pregnant patients with thyrotoxicosis. The clinical diagnosis of thyrotoxicosis in the pregnant woman may be difficult because of the similarity between hyper dynamic symptoms and signs frequently observed in euthyroid pregnant women and in thyrotoxicosis: fatigue, palpitations, anxiety, heat intolerance, and diaphoresis. A useful symptom is that, instead of the customary weight gain, patients report weight loss or, more frequently perhaps, the absence of weight gain despite an increased appetite (unless there is associated excessive vomiting). Nausea (morning sickness) occurs frequently during normal pregnancies. However, the occurrence of hyperemesis gravidarum accompanied by weight loss must always raise the possibility of thyrotoxicosis (30).

Owing to its transient nature, the clinical manifestations of gestational thyrotoxicosis are not always apparent or routinely detected. Symptoms compatible with thyrotoxicosis, including weight loss or the absence of weight increase, tachycardia and unexplained fatigue, are found in only one half of the women with gestational thyrotoxicosis (33).

CONCLUSIONS

1. The prevalence of gestational thyrotoxicosis among the study population was found to be 8.3 %.

2. There was a significant positive correlation between the levels of β-HCG and FT4 (p value < 0.05). Similarly a significant positive correlation between the levels of β-HCG and FT3 (p value < 0.05) was found.

3. There was a significant negative correlation between the levels of β-HCG and TSH levels (P value < 0.05).

4. There was no significant correlation between the severity of vomiting and the levels of FT3 ,FT4, TSH and β-HCG (All the p values > 0.05).

5. There was a high discordance rate in the thyroid profiles of the study subjects the commonest being low TSH with normal FT3/FT4 in fourteen patients (19.4%).

RECOMMEDATIONS

1) Strategy for screening of hyperthyroidism during pregnancy should be established. Women with emesis, fatigue, weight loss or absence of weight during pregnancy up to 16 weeks gestation should be screened for hyperthyroidism. This can be done by estimating the TSH and the FT4 levels in such patients.

2) The management protocol for gestational thyrotoxicosis should be determined. This can be done by determining the need of antithyroid drugs in patients with gestational thyrotoxicosis.

3) Studies to determine the effects of gestational thyrotoxicosis on the outcome of pregnancy should be carried out. Patients who have been proved to have gestational thyrotoxicosis in the early pregnancy should be followed-up to term so that the effects of the maternal thyroid hormones derangement on the fetus can be determined.

4) Further studies should be done on patients with severe vomiting during pregnancy (Hyperemesis gravidarum) only to determine whether there is any correlation with the thyroid hormones levels.

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QUESTIONNAIRE

Prevalence of Gestatinal Thyrotoxicosis in women with emesis during pregnancy

at Kenyatta National Hospital

1. Study Number:

2.   Name:

3. Age:

4. Parity

☐☐ + ☐☐

5. L.M.P.:

☐☐☐☐☐☐
D D M M Y Y

6. Gestation:

Medical History

6. Do you have any history of thyroid disease before pregnancy?   Yes/No

7. Did you have any of the following symptoms before pregnancy?

- Enlargement of the thyroid gland.   Yes/No

- Palpitations   Yes/No

- Heat/cold intorelance   Yes/No

- Weight loss   Yes/No

- Frequent diarrhoea/constipation   Yes/No

- Tremors   Yes/No

- Menstrual irregularities/disturbances   Yes/No

8. Do you have any history of chronic illness such as diabetes mellitus, tuberculosis cardiac failure or renal failure? Yes/No

9. Are you on any medications? Yes/ No

   If Yes which ones (List)

10. During this pregnancy have you had any of the following?

    - Unexplained fatigue.   Yes/No

    - Weight loss or absence of weight gain   Yes/No

    - Tarchycardia/palpitations   Yes/No

    - Nausea   Yes/No

    - Vomiting   Yes/No

11. How many times are you vomiting per day?

12. Apart from vomiting do you have any other medical symptoms?

1 (Yes)   2 (No)   3 (If yes which one)

Physical Examination

13. Temperature

14. Blood Pressure

   Diastolic

   Systolic

15. Pulse rate

16. Local examination of the thyroid gland, presence of Goiter. Yes/No

anaemia during Pregnancy in Kenyatta National Hospital

INFORMATION SHEET

Gestational transient thyrotoxicosis is a transient increase in thyroid secretion of non-autoimmune origin leading to thyrotoxicosis in pregnancy frequently in association with hyperemesis. This is a study aimed at determining the prevalence of hyperthyroidism in patient with vomiting during pregnancy. First an interview will be conducted and a questionnaire filled. Then about 4mls of blood will be collected once for analysis.

Risks and Benefits of this study

There is no obvious risk anticipated. The benefit include detection of any thyroid abnormalities that may be present. The results obtained in this study will be communicated to the attending doctor immediately for management of those who will have thyrotoxicosis and for follow-up of those who will be euthyroid. Determination of the prevalence of gestational thyrotoxicosis will also assist in the diagnosis of the condition among patients with emesis during pregnancy in future.

Informed consent

This study has been approved by the ethical and research committee of this hospital. The results of this test will be sent back to you through your doctor.

The blood samples as well as the results from this study will only be used for the above purposes and no other.

Confidentiality

Your identity will be kept strictly confidential throughout the study as well as during the publication of the study findings Your decision to participate or not to participate in this study will not affect the quality of your care.

Kindly fill the consent form below:

Patient information and consent form

A study on Prevalence of Gestational Thyrotoxicosis among women with emesis during Pregnancy in Kenyatta National Hospital

INFORMATION SHEET

Gestational transient thyrotoxicosis is a transient increase in thyroid secretion of non-autoimmune origin leading to thyrotoxicosis in pregnancy frequently in association with hyperemesis. This is a study aimed at determining the prevalence of thyrotoxicosis in patients with vomiting during pregnancy. First an interview will be conducted and a questionnaire filled. Then about 4mls of blood will be collected once for analysis.

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The blood sample as well as the results from this study will only be used for the above purposes and no other.

Confidentiality:

Your identity will be kept strictly confidential throughout the study as well as during the publication of the study findings. Your decision to participate or not to participate in this study will not affect the quality of your care.

Kindly fill the consent form below:

CONSENT FORM

I Mrs / Ms .... agree to enroll myself into

this study being fully aware of its purpose as explained to me by

.... and consent to the investigations.

Signature a) Participant/Relative..................... Date...........................

           b) Witness.................................Date...........................

For any concerns that you may have about the conduct of this study you may contact

any of my consultant supervisors below or Prof. K . M. Bhatt, chairperson of the

ethical and research committee at Kenyatta National Hospital.

SUPERVISORS

1. Dr. Zahida Qureshi   2. Dr. Angela Amayo

3. Prof. Christine Kigondu

Please contact Dr. J.R. Ndungu, the principal investigator of this study, on 0722673749 in case of any questions arising.

LABORATORY METHODS

Abbots IMX machine was used for the determination of serum TSH, FT3, FT4 and B-HCG levels.

DETERMINATION OF SERUM B-HCG

The IMX total B-HCG assay is based on the microparticle enzyme immunoassay technology The IMX total B-HCG reagents and sample are added to the reaction cell in the following sequence:

1. The probe assembly delivers the sample, IMX total B-HCG specimen diluent, anti-B-HCG:Alkaline phosphatase conjugate and anti-B-HCG coated microparticles into the incubation well of the reaction cell.

2. B-HCG binds to both the enzyme labeled antibody and the antibody coated microparticles forming an antibody-antigen antibody complex.

3. An aliquot of the antibody-antigen-antibody complex is transferred to the glass fibre matix to which the microparticles are irreversibly bound.

4. The matrix is washed to remove unbound materials.

5. The substrate, 4-methylumbelliferyl phosphate, is added to the matrix and the fluorescent product is measured by the MEIA optical assembly.

DETERMINATION OF FREE THYROXINE IN HUMAN SERUM

The IMX FT4 assay is based on the microparticle enzyme immunoassay technology The IMX FT4 reagents and sample are added to the reaction cell in the following sequence.

1. The probe assembly delivers the sample, and the anti FT4 coated microparticles into the incubation well of the reaction cell forming an antibody-T4 complex.

2. An aliquot of the reaction mixture containing T4 bound to the anti-T4 coated microparticles is transferred to the glass fibre matrix.

3. The matrix is washed with solubilizer solution to remove unbound materials.

4. The T4:Alkaline phosphatase conjugate is dispensed onto the matrix and binds to the unoccupied antibody binding sites.

5. The matrix is washed remove unbound materials

6. The substrate, 4-methylumbelliferyl phosphate, is added to the matrix and the fluorescent product is measured by the MEIA optical assembly.

DETERMINATION OF FREE T3 IN THE HUMAN SERUM

The IMX FT3 assay is based on the microparticle enzyme immunoassay technology The IMX FT3 reagents and sample are added to the reaction cell in the following sequence:

1. The probe assembly delivers the sample, and the anti FT3 coated microparticles into the incubation well of the reaction cell forming an antibody-T3 complex.

2. An aliquot of the reaction mixture containing T3 bound to the anti-T3 coated microparticles is transferred to the glass fibre matrix. The microparticles bind irreversibly to the glass fibre matrix.

3. The matrix is washed to remove unbound materials.

4. The T3:Alkaline phosphatase conjugate is dispensed onto the matrix and binds to the unoccupied antibody binding sites.

5. The matrix is washed remove unbound materials

6. The substrate, 4-methylumbelliferyl phosphate, is added to the matrix and the fluorescent product is measured by the MEIA optical assembly.

DETERMINATION OF TSH IN HUMAN SERUM

The IMX Ultrasensitive TSH assay is based on the microparticle enzyme immunoassay technology The IMX Ultrasensitive TSH reagents and sample are added to the reaction cell in the following sequence:

1. The probe assembly delivers the sample, and the anti TSH coated microparticles into the incubation well of the reaction cell.

2. The TSH binds to the Anti-TSH coated microparticles forming an antibody-antigen complex.

3. An aliquot of the reaction mixture containing antibody-antigen complex bound to the microparticles is transferred to the glass fibre matrix. The microparticles bind irreversibly to the glass fibre matrix.

3. The matrix is washed with wash buffer to remove unbound materials.

4. The anti-TSH:Alkaline phosphatase conjugate is dispensed onto the matrix and binds with the antibody-antigen complex.

5. The matrix is washed remove unbound materials.

6. The substrate, 4-methylumbelliferyl phosphate, is added to the matrix and the fluorescent product is measured by the MEIA optical assembly.

APPENDIX IV

LABORATORY RESULTS TABLE

PATIENT STUDY NUMBER:

	NORMAL	ABNORMAL
	1.LOW	2.HIGH

TSH LEVELS

FT3 LEVELS

FT4 LEVELS

HCG LEVELS

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Ref: KNH-ERC/01/2351

Date: 15 July 2004

Dr. Ndungu J R
Dept. of Human Pathology
Faculty of Medicine
University of Nairobi

Dear Dr. Ndungu

RESEARCH PROPOSAL "PREVALENCE OF GESTATIONAL THYROTOXICOSIS AMONG WOMEN WITH EMESIS DURING PREGNANCY IN KENYA NATIONAL HOSPITAL." (P61/5/2004)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** the revised version of your above cited research proposal for the period 15 July 2004 – 14 July 2005 You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication

Yours sincerely,

PROF. 'A N GUANTAI
SECRETARY, KNH-ERC

Cc   Prof. K M Bhatt, Chairperson, KNH-ERC
       The Deputy Director (C/S), KNH
       The Dean, Faculty of Medicine, UON
       The Chairman, Dept. of Human Pathology, UON
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