THYROID PROFILE IN AUB

This Dissertation is submitted for

MD DEGREE EXAMINATION

BRANCH II

OBSTETRICS AND GYNAECOLOGY

STANLEY MEDICAL COLLEGE

CHENNAI

Submitted to

THE TAMILNADU DR. MGR MEDICAL UNIVERSITY CHENNAI

SEPTEMBER 2006

BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"THYROID PROFILE IN AUB"** is a bonafide work of Dr.K.NARMADHA, Roll No. 20031557, who carried out the dissertation under my supervision. Certified further that to the best of my knowledge, the work reported herein does not form part of any other thesis or dissertation on the basis of which a degree or award was conferred on an earlier occasion on this or any other candidate.

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ACKNOWLEDGEMENT

I am greatly indebted to **Dr.M.VASANTHA,** MD, Dean, Stanley Medical College and Hospital, Chennai for permitting me to utilise the hospital facilities for conducting this study.

I am extremely grateful to **Dr.S.DEVAMBIGAI**, MD, D.G.O., Professor, HOD and Superintendent, Govt. RSRM Lying-In Hospital, Chennai for all her support.

I express my deep gratitude to **Dr.LATHA JAWAHAR**, MD, D.G.O., our former professor and Unit chief, Govt. RSRM Lying-In Hospital, Stanley Medical College who suggested this topic to me and for her valuable encouragement throughout my study.

I am thankful to all the Professors, Civil Surgeons and Assistant Civil Surgeons of Govt. RSRM Lying-In Hospital, for their invaluable help in every step during this study.

I would especially like to thank **Dr.SHANTHA**, MD, Professor and HOD, Department of Immunology for her valuable guidance.

I thank **Mr.VENKATESAN**, M.Sc., PGDCA, Lecturer in Statistics, Clinical Epidemiology Unit, Govt. Stanley Medical College, for his patient guidance in statistical analysis of the study data.

My sincere thanks to my family and friends for their moral support and encouragement.

I will be failing in my duty if I do not express my sincere thanks to all the patients for the consent and cooperation they extended for this study.

CONTENTS

INTRODUCTION

Today, women experience ten times more menstrual cycles than their ancestors did. Over the years menorrhagia has become an increasingly frequent complaint. This may be attributed to the increased availability of effective contraception, decreased tolerance of the inconvenience of menorrhagia and higher expectations of the health service.

The social and economic cost of menorrhagia is considerable. Nearly 28% of female population consider their menstruation excessive. Nearly 10% of employed women will need to take time off work because of excessive menstrual loss (Edmund M et al, 1994). Annually, 30% of hysterectomies are carried out for menstrual disturbances alone (Coulter et al, BJOG, 1991). Menorrhagia is the main cause of iron deficiency anaemia in women in developed countries (Beazly JM, 1992).

Thyroid dysfunction is a common cause of AUB and accounts for 30-40% of cases (Koutras DA, 1997). Thyroid disorders are 10 times more common in women than men (Sisan et al, 1987). Approximately 1% of the female population will develop overt hypothyroidism (Turnbridge WMG, 1977). Abnormal menstrual cycles are occasionally the first sign of hypothyroidism or hyperthyroidism.(Wilansky DL, Griesman B, 1992).

The clinical objective is to detect and treat thyroid disease before the symptoms and signs are significant and intense. Therefore the key to early diagnosis is to maintain a high index of suspicion and to readily screen for the presence of abnormal thyroid function. Moreover, thyroid dysfunction is an easily correctable cause of AUB. Appropriate treatment is rewarded by the prompt return of normal menstrual cycles.

AIM OF THE STUDY

The study is aimed at a cross-section of population presenting to the Department of Obstetrics and Gynaecology at the Government RSRM Lying-in Hospital, Stanley Medical College with complaints of abnormal uterine bleeding. The study aims to ascertain the following:

1) Possibility of association between thyroid dysfunction and AUB in the reproductive age group (18-45 years).

2) To study the thyroid profile in different types of AUB in the reproductive age group.

3) To establish if screening for thyroid abnormalities is justified using T_4 and TSH.

REVIEW OF LITERATURE

1. Gardner and Hill in 1927 showed an association between hypothyroidism and menorrhagia.

2. Goldsmith et al in 1952 found that 8 out of 10 patients with hypothyroidism had ovulatory failure with only 2 experiencing normal ovulation and menses.

3. Rogers et al in 1958 stated that the most common abnormality observed by hypothyroid women is a change in the character of uterine bleeding and length of the cycle.

4. Scott in 1964 found that 56% of women with hypothyroidism had abnormal menstrual patterns with menorrhagia being the most common.

5. Blum and Blum in 1972 have studied the relationship between subclinical hypothyroidism and menorrhagia.

6. Geenspan et al in 1975 advocated the empirical use of the thyroxine. But in 1999, Prentice et al have stated that the empirical use of thyroxine is controversial. They have condemned it and advocated the use of TRH in women with AUB and normal T_3, T_4, and TSH.

7. Akande in 1975 stated that changes in FSH/LH ratios caused anovulatory cycles in hypothyroidism.

8. Andrew Weeks in 1987 in his study of 650 women with menstrual

disturbances at the Jessop hospital has stated that hypothyroidism is a greatly underdiagonised cause of menorrhagia.

9. Keye WR, Yuen B Knopff in 1976 have stated that hyperprolactinemia causing luteal phase defect is asociated with less severe forms of hypothyroidism.

10. Robuschi et al in 1987 have stated that hypothyroidism increases with age and is more common in older women. Upto 45% of thyroid glands from women over 60 show evidence of thyroiditis. The incidence of anti-thyroglobulin antibodies is 7.4% in women over age 75 while 16.9% of women aged 60 and 17.4% of women over age 75 have elevated TSH levels. In women admitted to geriartric wards, 2-4 % have clinically apparent hypothyroidism.

11. Klee et al in 1987 have shown the significance and positive predictive value of TSH assay in thyroid function tests. They are of opinion that TSH based testing strategies minimise the problem of abnormal T_4 study and significantly reduce the number of TRH stimulation tests performed.

12. Smith et al in 1987 showed an association between hypothyroidism and menorrhagia with development of an advanced form of Von Willebrands' disease in untreated hypothyroidism. The hemostatic defects returned to normal with thyroxine supplementation.

13. Bleney et al in 1990 confirmed the findings of Smith et al.

14. Hingham in 1992 reported a case of hypothyroidism in which the menstrual

loss was measured. An initial loss of 480 ml decreased to 58 ml following a 3 month treatment with thyroxine.

15. Wilansky et al in 1992 performed thyrotropin releasing hormone (TRH) test in 67 women who complained of excessive menstrual loss. All had normal levels of thyroxine and thyroid stimulating hormone (TSH). They found that 22% had abnormal TRH tests and they treated these women with thyroxine. At follow up between 12 and 36 months later, all considered their menstrual loss to be normal. In the 16 women with normal TRH tests, 56% still complained of menorrhagia.

16. Blum and Blum in 1992 studied the possible relationship between menorrhagia and occult hypothyroidism in IUD-wearing women. They studied 40 women with menorrhagia secondary to an intrauterine contraceptive device. They all had normal free thyroxine and TSH levels. The 10 patients who had the highest TSH levels were given a TRH test and all proved to have early hypothyroidism. All patients reported a significant improvement with thyroxine treatment. This recent development deserves further study.

17. Danese MD et al in 1996 have stated that hypothyroidism is frequent enough to warrant consideration in most older women. They recommend screening with highly sensitive TSH assay every 5 years beginning at age 35 and then every two years beginning at age 60 or with the appearance of any symptom suggesting hypothyroidism.

18. Chameron and Fraser in 1998 in their study on the clinical disorders of

the endometrium and the menstrual cycle have stated that thyroid disorders are the most common endocrine abnormality associated with menstrual disturbances. Hypothyroidism is a potent cause of menorrhagia which is amenable to treatment.

19. Shaw RW in 1999 conducted a large comparitive analysis to study the effect of thyroxine replacement on menstrual blood loss in hypothyroid patients. There was a relative improvement in haemoglobin concentration and general condition of the patients.

20. Prentice et al - Medical Management of Menorrhagia - 1999 have stated that all women with unexplained menorrhagia should be tested for thyroid dysfunction.

The review of literature suggests that there is a strong correlation between AUB and thyroid dysfunction. It stands as an easily correctable cause of AUB.

PHYSIOLOGY OF MENSTRUATION

Menstruation is a very recent phenomenon in the evolutionary time line. It occurs in very few species even among viviparous animals. The diagnosis and management of abnormal menstrual function must be based on an understanding of the physiologic mechanisms involved in the regulation of the normal cycle. Although the activity of the endometrium is directly controlled by the ovarian function and by the two hormones secreted by the ovary, the ovary itself is activated by the pituitary gland, the secretion of which is under the nervous control of the hypothalamus.

The normal human menstrual cycle can be divided into two segments : the ovarian cycle and the uterine cycle based on the organ under examination. The ovarian cycle maybe further divided into follicular and luteal phases, whereas the uterine cycle is divided into the corresponding proliferative and secretory phases.

(1) At the beginning of each monthly menstrual cycle, levels of gonadal steriods are low and have been decreasing since the end of the luteal phase of the previous cycle.

(2) With the demise of the corpus luteum, FSH levels begin to rise and a cohort of growing follicles is recruited. These follicles each secrete increasing levels of oestrogen as they grow in the follicular phase. This, in turn, is the stimulus for uterine endometrial proliferation.

(3) Rising oestrogen levels provide a negative feed back on pituitary

FSH secretion which begins to wane by the midpoint of the follicular phase. Conversely, LH initially decreases in response to rising estradiol levels but late in the follicular phase the LH level is increased dramatically (biphasic response).

(4) At the end of the follicular phase (just prior to ovulation), FSH induced LH receptors are present on granulosa cells and with LH stimulation, modulate the release of progesterone.

(5) After a sufficient degree of oestrogenic stimulation, the pituitary LH surge is triggered, which is the proximate cause of ovulation which occurs 24-36 hours later. Ovulation heralds the transition to luteal-secretory phase.

(6) The oestrogen level decreases through the early luteal phase from just before ovulation until the midluteal phase when it begins to rise again as a result of corpus luteum secretion.

(7) Progesterone levels rise precipitously after ovulation and can be used as a presumptive sign that ovulation has occured.

(8) Both oestrogen and progesterone levels remain elevated throughout the life of the corpus luteum and then wane with its demise, thereby setting the stage for the next cycle.

(9) In the absence of implantation, glandular secretion ceases and an

irregular breakdown of the decidua functionalis occurs. The result is a shedding of this layer of the endometrium, a process termed menses.

The Normal Menstrual Cycle

A normal menstrual cycle lasts from 21 to 35 days with 2 to 6 days of flow and an average blood loss of 20-60 ml. (Vollman RF, 1977 and Treloar AE, 1967). However studies of large numbers of women with normal menstrual cycles have shown that only approximately two-thirds of adult women have cycles lasting 21-35 days (Friedman E, 1977). The extremes of reproductive life are characterised by a higher percentage of anovulatory or irregularly timed cycles (Collett ME et al, 1954).

DEFINITION OF MENSTRUAL CYCLE IRREGULARITIES

(1) Oligomenorrhea :

Infrequent, irregularly timed episodes of bleeding usually occuring at intervals of more than 35 days.

(2) Polymenorrhea :

Frequent but regularly timed episodes of bleeding usually occuring at intervals of 21 days or less.

(3) Menorrhagia :

Regularly timed episodes of bleeding that are excessive in amount (> 80 ml) and duration of flow (>5 days).

(4) Metrorrhagia :

Irregularly timed bleeding.

(5) Menometrorrhagia :

Excessive, prolonged bleeding that occurs at irregularly timed, frequent intervals.

(6) Hypomenorrhea :

Regularly timed bleeding that is decreased in amount.

(7) Intermenstrual bleeding : bleeding (usually not of an excessive amount) that occurs between otherwise normal menstrual cycles.

(8) Amenorrhea : Absence of menstruation for three normal cycles or six months.

THE THYROID GLAND

Thomas Wharton in 1656, gave the thyroid gland its modern name. For unknown reasons, thyroid disease is more common in women than in men (Medvei VC, 1993).

Normal Thyroid Physiology

Thyroid hormone synthesis depends on an adequate supply of iodine in the diet. It is absorbed as iodide and enters the thyroid under the influence of TSH. Within the gland iodide is oxidised to elemental iodine which is then bound to tyrosine. Mono and di-iodotyrosines combine to form thyroxine (T_4) and Tri-iodothyronine (T_3) (Norman AW, Litwack G, 1987). These compounds are part of the thyroglobulin molecule which serves as a storage depot for the thyroid hormone. TSH induces a proteolytic enzyme that results in the release of iodothyronines into the bloodstream as thyroid hormone. Removal of one iodine from the phenolic ring of T_4 yields T_3.

One-third of T_4 secreted each day is converted in the peripheral tissues, largely in the liver and kidney to T_3 and about 40% is converted into inactive Reverse T_3. Although T_4 in secreted at 20 times the rate of T_3, T_3 is responsible for most of the thyroid action in the body (Czarnocka B et al, 1985).

Mechanism of Thyroid Hormone Action

Thyroid hormone acts by binding to a specific nuclear DNA bound thyroid hormone receptor (TR) usually as a heterodimer with the retinoid X receptor (RXR) at specific sequences dictated by the DNA binding site preferences of the RXR-TR complex. T_3 has a 15 fold higher binding affinity for TR than does T_4 which explains its function as the active thyroid hormone (Brent GA, 1994).

Bound and Free fractions of Thyroid Hormones

Thyroid hormones present in circulation are mainly bound to proteins. Approximately 70% of thyroid hormones are bound to thyroxine binding globulin (TBG). The remaining 30% is bound to thyroxine binding prealbumin and albumin. The binding proteins have greater affinity for T_4 and thus allow T_3 to have a greater entry into the cells. TBG is synthesised in the liver and the synthesis is increased by oestrogens.

Regulation of thyroid hormone secretion - Role of estrogens

Thyroid hormones regulate TSH secretion by supressing TRH secretion,

but primarily affect the pituitary sensitivity to TRH, by reducing the numbers of TRH receptors. Pituitary secretion of TSH is very sensitive to changes in the circulating level of thyroid hormone. A slight change in the circulating level of T_4 will produce a many fold greater response in TSH. TSH secreting cells are regulated by T_4 but only after the T_4 is converted to T_3 in the pituitary cells. Although some tissues depend mainly on the blood T_3 for their intracellular T_3, the brain and pituitary depend on their own intracellular conversion of T_4.

The measurement of T_4 and TSH therefore provides the most accurate assessment of thyroid function.

The TSH response to TRH is influenced mainly by the thyroid hormone concentration in the circulation. Estrogen increases the TRH receptor content in the pituitary. Hence the TSH response to TRH is greater in women than in men and greater in women taking oral contraceptives.

The smallest doses of the TRH that are capable of producing an increase in TSH also increase the prolactin levels indicating a physiologic role for TRH in the control of prolactin secretion.

Thyroid Function Tests

Serum thyroid hormones are measured by radio-immunoassay. Conditions that elevate the TBG (pregnancy, oestrogen replacement, use of oral contraceptive pills, hepatitis) necessitate measurement of T_3 resin uptake for clarification.

(1) Free Thyroxine (FT_4): Assays that measure free T_4 are usually displacement assays using an autoantibody to T_4. The result is not

affected by changes in TBG and binding.

(2) **Total Thyroxine (TT_4)**: The total thyroxine, both the portion bound to TBG and the free unbound portion is measured by displacement assays and in the absence of hormone therapy and other illnesses estimates the thyroxine concentration in the blood.

(3) **TSH** : TSH is measured by highly sensitive assays than can detect concentrations as low as 0.01 μu/L. This is a very sensitive indicator of thyroid hormone action at tissue level because it is dependent on the pituitary exposure to T_4. In the absence of hypothalamic or pituitary disease, the sensitive TSH assays will provide the best indication of excess or deficient thyroxine. Slight changes in T_4 are reflected in a many fold greater response in TSH. Transient changes in TSH are seen in severe systemic illness, psychiatric illness, adrenal insufficiency, corticosteroid therapy, elevated hCG (Since hCG can stimulate the TSH receptor) and in any acute illness.

(4) **Total T_3 and Reverse T_3** : These are rarely required for the accurate evaluation of a patient with an abnormal TSH level and are of little value in clinical circumstances. Serum T_3 is almost always an indirect reflection of the serum T_4 supply (Berghout A, 1994).

Other tests include the free thyroxine index and radioactive iodine uptake.

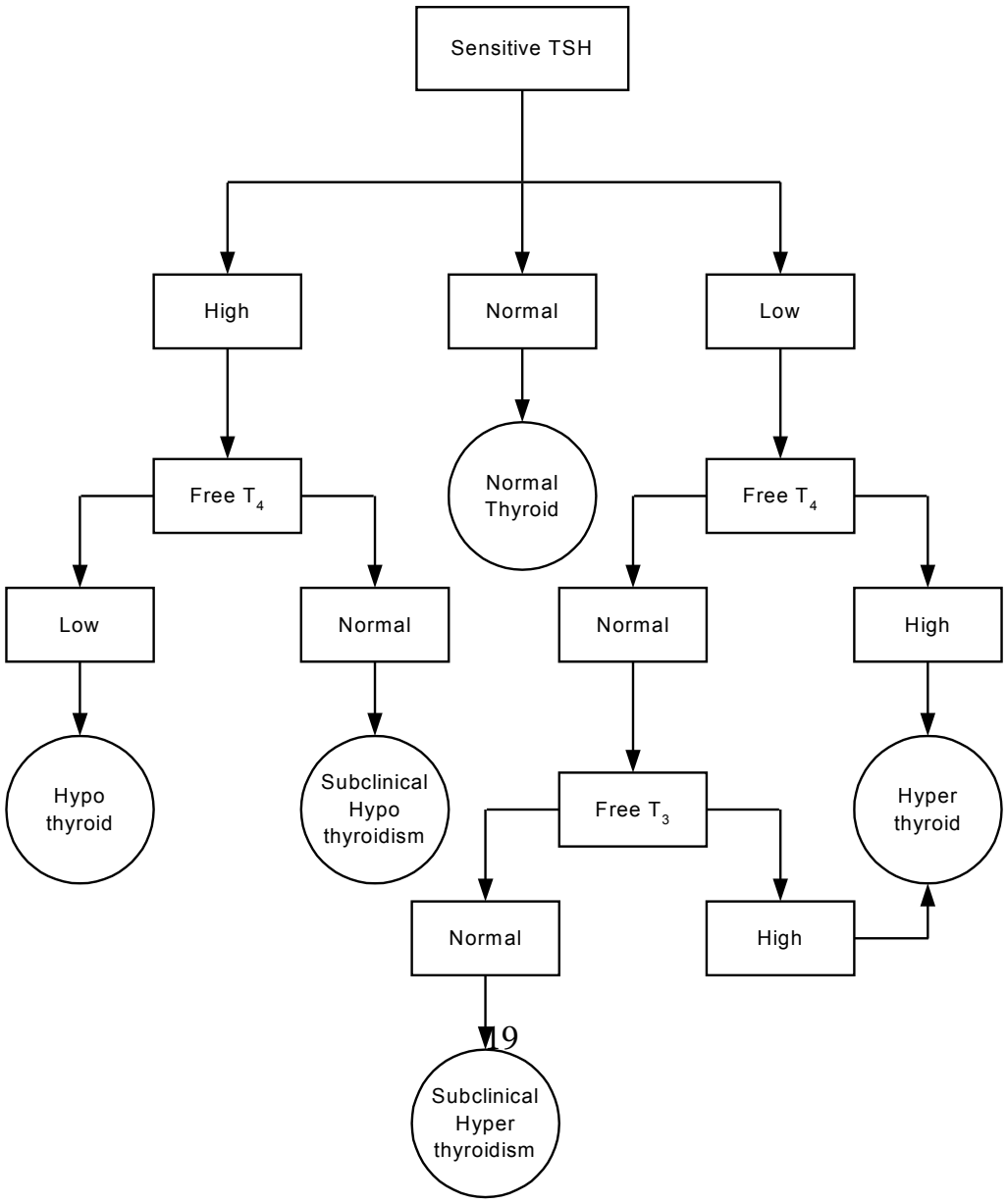
THE LABORATORY EVALUATION

For screening purposes or when there is a relatively low clinical suspicion of thyroid disease, the initial step is to measure the TSH by a

sensitive assay. A normal TSH essentially excludes hypo / hyperthyroidism. A high TSH requires the measurement of free T_4 to confirm the diagnosis of hypothyroidism. If the initial TSH is low, especially less than 0.08 μu/ml, then measurement of a high T_4 will confirm the diagnosis of hyperthyroidism. If T_4 is normal, the T_3 level is measured since some patients will have predominantly T_3 toxicosis.

If T_3 is normal it implies that thyroxine secretion is autonomous from TSH and this is called subclinical hyperthyroidism. Some of these patients will eventually have increased T_4 or T_3 levels with true hyperthyroidism.

The algorithm represents a cost-effective and accurate clinical strategy.



(Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon, TH American Thyroid Association guidelines for use of laboratory tests in thyroid disorders, JAMA 263: 1529,1990).

Role of Thyroid in Reproductive Physiology / Pathology

The following facts emphasis the role of thyroid hormone in the female reproductive physiology.

(1) TSH receptors have been found on granulosa cells.

(2) T_3 and T_4 have been found in follicular fluids.

(3) T_4 has been found to enhance the action of gonadotrophins in luteinisation and progesterone secretion.

The female hormonal milieu and its potential effects on immune surveillance undoubtedly play a role in the increased risk (10 fold) of women to develop autoimmune thyroid disease (Gaitan E et al, 1985 and Wenzel BE et al, 1987). The immunoglobulins produced against the thyroid are polyclonal and the multiple combinations of various antibodies present combine to create the clinical spectrum of autoimmune thyroid diseases that affect successful reproductive function.

Foetal and neonatal period

Very few data exist regarding the role of the thyroid hormones in the reproductive system of the foetus. No effective human studies are available Thyroid excess in mice is shown to cause early maturation of the reproductive tract and early opening of the vagina. Hypothyroidism in mice causes small ovaries deficient in cholesterol. No change has been observed in human foetuses.

Hypothyroidism

(1) Prepubertal / Pubertal

In both sexes, thyroid hormones influence sexual development and reproductive function.

Infantile hypothyroidism, if untreated, leads to sexual immaturity. Juvenile hypothyroidism causes a delay in the onset of puberty followed by anovulatory cycles.

Paradoxically primary hypothyroidism may also cause precocious sexual development and galactorrhea. (Kleinberg DL, New England J. Med. 1977). The McCune Albright syndrome is characterized by hyperfunctioning endocrinopathies including hyper/hypothyroidism and sexual precocity, but the association may be coincidental (Albright F, Maine MJ, 1938). Precocious puberty with delayed bone age suggests primary hypothroidism. Serum TSH is increased, T_4 is low and galactorrhea maybe present with increased serum prolactin (Honbo KS et al, 1978). Kindle et al have described a syndrome of precocious menstruation, galactorrhea and sella enlargement in girls with

juvenile hypothyroidism.

2. In adult women

Severe hypothyroidism in associated with diminished libido, amenorrhea or anovulation (Grodstein F et al, 1993). Secretion of progesterone is inadequate and endometrial proliferation persists resulting in excessive and irregular breakthrough menstrual bleeding. These changes may be due to deficient secretion of luteinizing hormone. Rarely in primary hypothyroidism, secondary depression of pituitary function may lead to ovarian atrophy and amenorrhea. Hypothyroidism appears to be associated with decreased fertility resulting from ovulatory difficulties, and spontaneous abortions may result, although many pregnancies are successful. (Lao TTH et al, 1988 and Morimotoc et al, 1990).

The values for plasma gonadotrophins are usually in the normal range in primary hypothyroidism. In postmenopausal women, levels are usually lower than euthyroid women of the same age but are nevertheless within the menopausal range. This provides a valuable means of differentiating primary from secondary hypothyroidism (Melmed S, Hershman J, 1982).

Myxedematous infiltration can produce enlarged, cystic ovaries (Kansen KA et al, 1997).

There may be a high incidence of early or potential hypothyroidism in women presenting with menorrhagia. Hypothyroidism can cause menorrhagia / polymenorrhea - these symptoms being present in 30 - 40% of the cases.

(Koutras DA, 1997).

Metabolism of oestrogens in hypothyroidism

The metabolism of oestrogens is also altered. With respect to oestradiol and oestrone, hypothyroidism favours the metabolism of these steroids via 16-α-hydroxylation over that via 2-oxygenation with the result that the formation of oestriol is increased and that of 2-hydroxyoestrone and its derivative 2- methoxyoestrone is decreased. The sex hormone binding globulin (SHBG) concentrations in plasma is decreased with the result that the plasma concentrations of both testosterone and oestradiol are decreased, but the unbound fractions are increased. The alterations in steroid metabolism are corrected by restoration of the euthyroid state (Brenta GA, et al, Variations of SHBG in thyroid dysfunction, 1999).

Effects of hypothyroidsm on the GnRH pulsatality.

TSH is secreted by the pituitary and its excess production causes menstrual abnormality due to its adverse effects on the GnRH pulse generator and not by directly affecting the ovary. When there is decrease in GnRH pulsatality, anovulation can occur. Even slight changes in pulsatality may result in luteal phase defect (Del Pozo, 1979 and Warfel W, 1992).

Primary hypothyroidism and hyperprolactinemia

Hyperprolactinemia and anovulation may be associated with primary hypothyroidism. Remarkable enlargement of the pituitary with thyrotroph hyperplasia and hyperprolactinemia is frequently seen in long standing primary

hypothyroidism (Franks et al, 1975).

A number of mechanisms may be involved:

1) The clearance of prolactin tends to be decreased in hypothyroidism (Warfel W, 1992).

2) Patients with severe hypothy+roidism may have elevated total and free estradiol levels giving rise to increased prolactin production stimulated by excess free oestrogen. (Tolis G et al, 1979).

3) The third and the most significant mechanism involves the inhibitory effects of T_3 on TRH production and on TRH receptor expression. A decrease in the T_3 feedback in hypothyroidism may induce an increase in the hypothalamic TRH production and in the number of TRH receptors in the lactotroph. Increased TRH action on the lactotroph in turn may stimulate prolactin secretion (Collu R, 1986).

   The duration of hypothyroidism is important with regard to the mechanism of amenorrhea — the longer the duration, the higher the incidence of amemorrhea and higher the prolactin levels. This may be associated with decreasing hypothalamic content of dopamine with ongoing hypothyrodism. This would lead to an unopposed TRH stimulatory effect on the pituitary cells that secrete prolactin. Constant stimulation by the hypothalamic releasing hormones can result in hypertrophy or hyperplasia of the pituitary (Keye) WR,1976).

Subclinical Hypothyroidism

This term designates a situation in which an asymptomatic patient has a low normal FT_4I (free thyroxine index) but a slightly elevated serum TSH level. The TSH elevation in these patients is modest with values typically between 5 and 15 mu/L. It occurs in 7-10% of women.

Effects of Hyperthyroidism on Reproductive function

The two primary causes of hyperthyroidism are Grave's disease (toxic diffuse goiter) and Plummer's disease (toxic nodular goiter) (Lazarus JH in Lancet 349,1997). Thyrotoxicosis in early life may cause delayed sexual maturation although physical development is normal and skeletal growth maybe accelerated Menstural changes associated with hyperthyroidism are unpredictable, ranging from amenorrhea to oligomenorrhea and normal cycles. The intermenstrual interval maybe prolonged or shortened, menstrual flow is initially diminished and ultimately ceases (McKenzie JM, 1979). Fertility maybe reduced and the risk of miscarriage is increased. In some patients menstrual cycles are predominantly anovulatory with oligomenorrhea. In most patients, however, ovulation occurs as is indicated by the secretory endometrium (Reid RL, 1987). Hyperthyroidism seldom causes amenorrhea unless exophthalmos is present.

The mechanisms involved may be the following.

(1) Increased SHBG levels decrease the clearance of testosterone and estradiol. Increased peripheral aromatisation of androgens gives rise to oestrogens due to the increase in peripheral blood flow (Thomas

R, 1987).

(2) Another more likely mechanism is the disruption in the amplitude and frequency of LH /FSH pulses due to thyroid hormone influences on GnRH signalling (DeGroot N, 1979).

Subclinical Hyperthyroidism

The presence of a chronically sepressed serum TSH level with peripheral free thyroid hormones in the normal range is called subclinical hyperthyroidism. The incidence is 0.9%. Progression to overt hyperthyroidism is uncommon. The incidence increases in older women (Felicetta JU, 1987).

Screening for primary hypothyroidism

Only a few patients with amenorrhea/ galactorrhea will have hypothyroidism that is not clinically apparent. Although it seems extravagant to measure the TSH in such a large number of patients for such a small return, because the treatment of hypothyroidism is so simple and is rewarded by a prompt return of menstrual cycles, TSH measurement is warranted (Caldwell G, 1985).

The high incidence of hypothyroidism in women, particularly if the 7-10% prevalance of subclinical hypothyroidism is included raises the issue of whether the cost of systematic periodic screening of an asymptomatic population is justified (Westman AP, BMJ, 1997). The conclusions depend to a great extent, on the assumptions regarding the effectiveness and economic value of therapy in asymptomatic patients with TSH elevation alone. An assessment of TSH levels at 5 year intervals in older women (greater than 50

years) seems justified, but further analysis of more extensive screening programs are in order (P. Reid Larsen and Terry F. Davies, 2003).

Prediction of disease onset

Patients with increased TSH and normal T_4 levels progress to overt thyroid failure at a rate of about 5% per year if thyroid auto antibody levels are elevated. If the serum TSH alone is elevated witout positive thyroid antibody titres, the annual risk for hypothyroidism drops to approximately 3% per year. Most clinicians therefore treat women who have elevated serum TSH concentrations and positive thyroid antibody tests even in the absence of symptoms. (Vanderpump MPJ, Turnbridge WMG, 1996).

Thyroid dysfunction and menstrual disturbances in specific conditions

1) Anorexia nervosa

The various problems associated with anorexia represent a dysfunction of the body mechanisms regulated by the hypothalamus. Anorexics are usually amenorrhic. Many symptoms can be explained by the state of relative hypothyroidism. There appears to be a compensation for the state of malnourishment with diversion from the formation of active T_3 to the inactive metabolite reverse T_3 - a state of chemical hypothyroidism (Herzog DB, Copeland PM, 1985)

2) Exercise and stress induced amenorrhea

In patients with exercise induced amenorrhea, there is a decrease in the frequency of GnRH pulses which is assessed by measuring a decrease in the frequency of LH pulses (Olson BR, 1989). Atheletes have relatively low T_4 levels but amenorrhic atheletes have an overall supression of all circulating thyroid hormones including reverse T_3. These patients are usually hypoestrogenic, but less severe alterations may cause minimal menstrual dysfunction (anovulation / luteal phase defect) (Gennazzani AR et al, 1991).

3) Turners Syndrome

Patients with Turners, characterised by 45 XO Karyotype have a short stature, primary amenorrhea and other abnormalities. A high prevalance of autoimmune thyroid disorders is noted. Approximately 50% of adult patients with Turners have anti-thyroid peroxidase (anti-TPO) and antithyroglobulin (anti TG) antibody. Approximately 30% will develop subclinical/ clinical hypothyroidism (Barbesino G et al, 1998).

4) Postpartum thyroiditis

Transient thyrotoxicosis may develop within 3-6 months after delivery and is often followed by a period of hypothyroidism of several months duration with an eventual return to euthyroid state (Amino N, 1982). In some patients, only a hypothyroid phase is apparent. Data suggest that 8-10% of women experience thyroiditis in the postpartum period (Hayslip et al, 1988). Pregnancy is therefore an important risk factor with transient thyroiditis developing in some patients and thyroid failure developing permanently or in the early years after pregnancy in a significant proportion.

MATERIALS AND METHODS

The present study of "Thyroid Profile in AUB" was conducted in Govt. R.S.R.M. Lying-in Hospital, attached to Govt. Stanley Medical College, Chennai. This is a cross-sectional study of 250 women with AUB, based on data collected from women with AUB attending the out-patient department and in-patients during a period of 8 months from May 2005 to December 2005 at this hospital. The study group included women with the following complaints.

1) Oligomenorrhea : Cycle length greater than 35 days.

2) Hypomenorrhea : Bleeding lasting less than 2 days.

3) Menorrhagia : Blood loss greater than 60 ml or more than 6 pads / day associated with clots.

4) Polymenorrhea : Cycle length less than 22 days.

5) Amenorrhea : Absence of menstruation for 6 months or 3 consecutive menstrual cycles.

Inclusion Criteria

(1) Women in the age group of 18-45 years.

(2) Women with any of the menstrual disturbances mentioned above.

(3) Women who do not have signs of demonstrable pelvic pathology including PID.

(4) Women with increased BMI.

(5) Women who are not on any hormonal preparation.

(6) Women who were not using any IUCD in the past two years.

(7) Women who have not had any thyroid replacement therapy.

(8) Women with signs and symptoms of hypo/ hyperthyroidism.

Exclusion Criteria

(1) Teenage AUB.

(2) Age greater than 45 years.

(3) Presence of palpable pelvic pathology like fibroids, polyps or cervical growths.

(4) Presence of general disorders like tuberculosis.

(5) Presence of diabetes, hypertension or clotting abnormalities .

(6) Patients with history of bleeding diatheses.

(7) Patients on drugs like aspirin, heparin, sulpha drugs, antithyroid medication, eltroxin, glucocorticoids, and amiodarone.

Symptoms and Signs of hyperthyroidism.

(1) Weight loss greater than 10 kg in 3 months or subjective weight loss

(2) Diarrhoea

(3) Heat intolerence

(4) Tremors

(5) Tachycardia

(6) Eye changes - exophthalmos

Symptoms and signs of hypothyroidism

(1) Weight gain of more than 10 kg in 3 months or subjective weight gain

(2) Constipation

(3) Slow mentation / lethargy / increased sleepiness.

(4) Elevated cholesterol

(5) Coarse skin.

PROCEDURE

Patients were selected based on the above criteria and history was taken as per the proforma including a detailed menstrual history and questions regarding the signs and symptoms, of hypothyroidism and hyperthyroidism. The following examination was done.

A detailed general examination focussing specifically on the presence/ absence of anaemia, thyroid swelling, cardiovascular abnormality, gross nervous system dysfunction, galactorrhea and abnormal hair distribution. The height in centimeters and weight in kilograms was measured and the BMI calculated. An abdominal, speculum examination and pelvic examination were done to rule out other causes of abnormal bleeding. 5 ml of venus blood was taken in a dry plain glass container without any anticoagulant for TSH assay and T_4 estimation. Morning sample in the fasting state was taken.

TSH assay was performed using ultrasensitive solid phase-two site immunoradiometric assay (IRMA). IRMA-K9 kit supplied by Board of Radiation and Isotope Technology (BRIT), Bombay was used. The physiological range was 0.3 - 6.18 μIU/ml with due consideration given to dional / pulsatile variation.

T_4 was analysed using RIA K-5/5A kit supplied by BRIT, Bombay. The physiological range was 4.8 to 11.5 μg / dl.

ANALYSIS OF THE STUDY - OBSERVATIONS

TABLE - 1

AGE DISTRIBUTION OF THE STUDY GROUP

Age group	Frequency	Percentage
18-24	32	12.8%
24-32	142	56.8%
32-40	51	20.4%
>40	25	10%

Majority of the patients belonged to the age group of 24 - 32 years

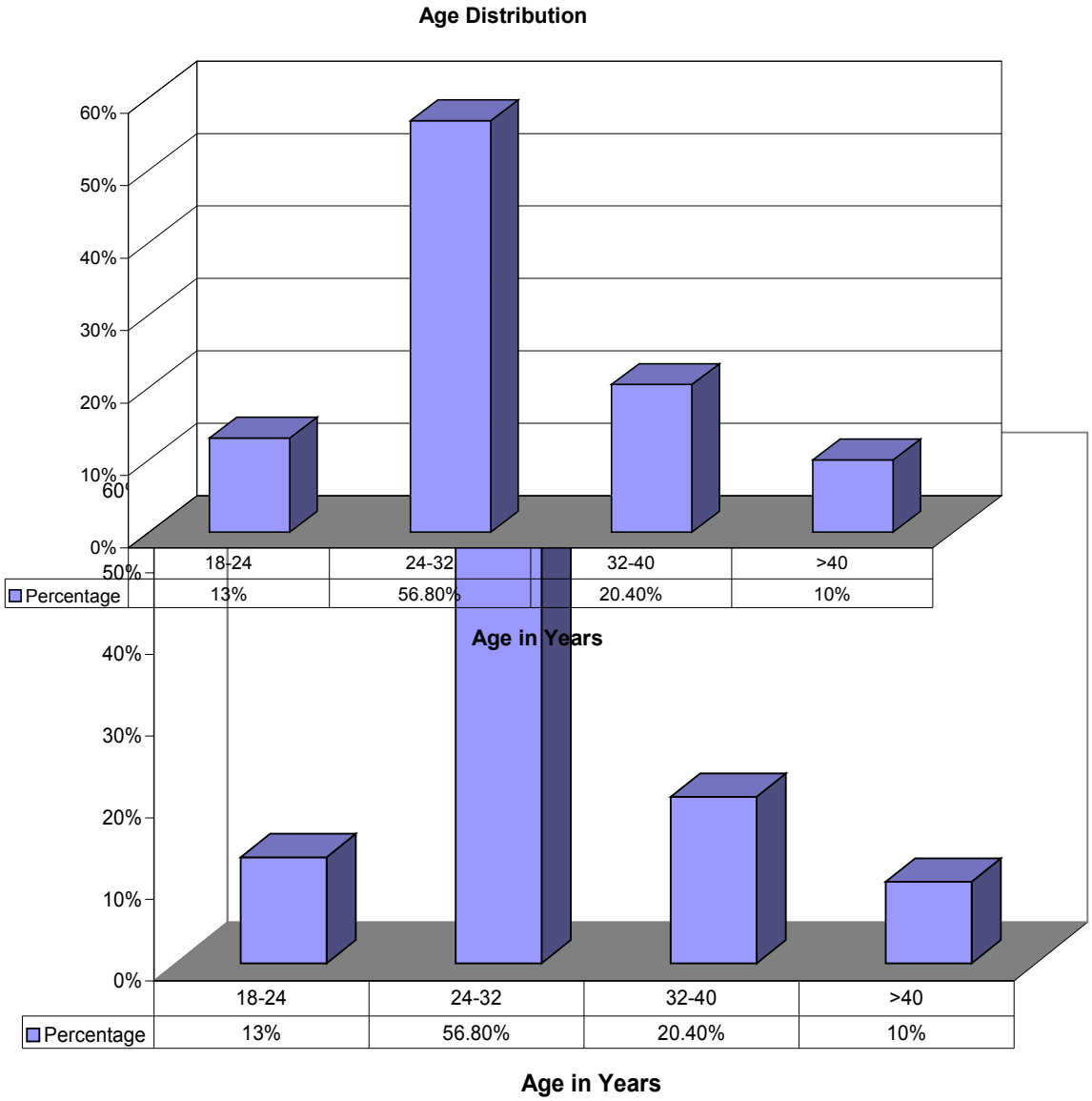


TABLE - 2

PARITY OF THE STUDY GROUP

Parity	Frequency	Percentage
Nullipara	23	9.2%
P_1L_1	65	26%
P_2L_2	112	44.8%
Multipara	50	20%

Majority of the patients in the study group were P_2L_2

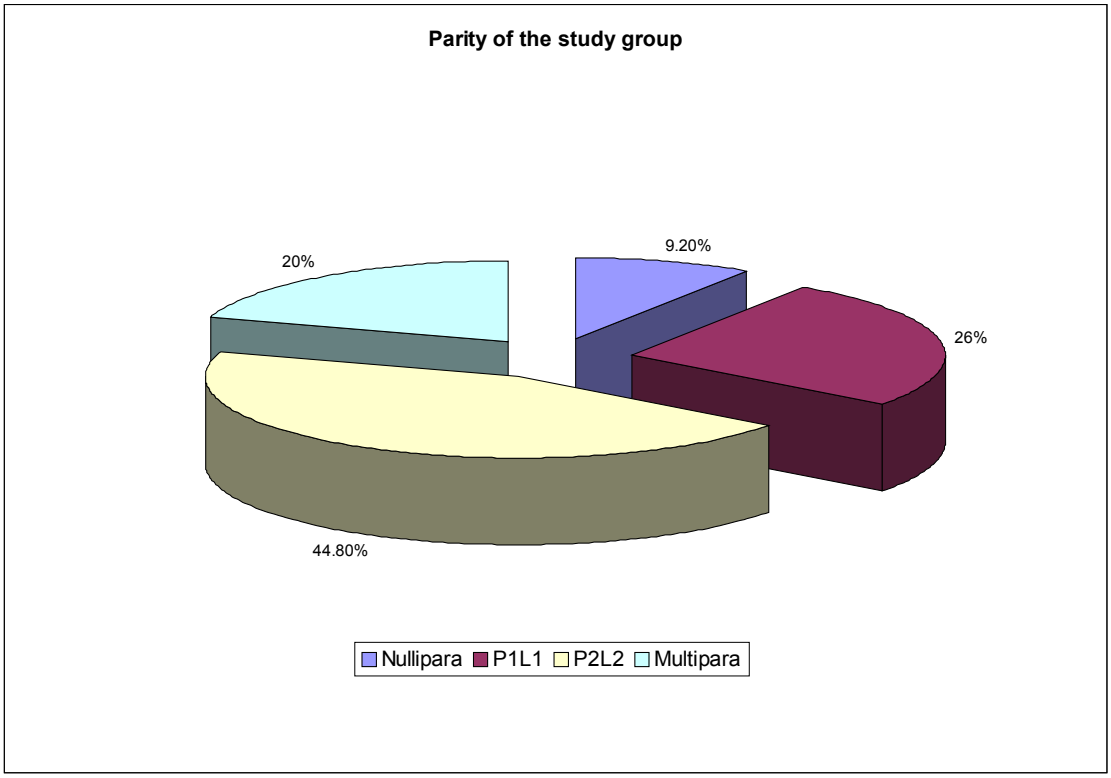


TABLE - 3

TYPE OF AUB

Type of AUB	Frequency	Percentage
Oligomenorrhea	78	31.2%
Menorrhagia	110	44.0%
Amenorrhea	78	19.6%
Hypomenorrhea	7	2.8%
Polymenorrhea	6	2.4%

Majority of patients in the study group had menorrhagia and oligomenorrhea

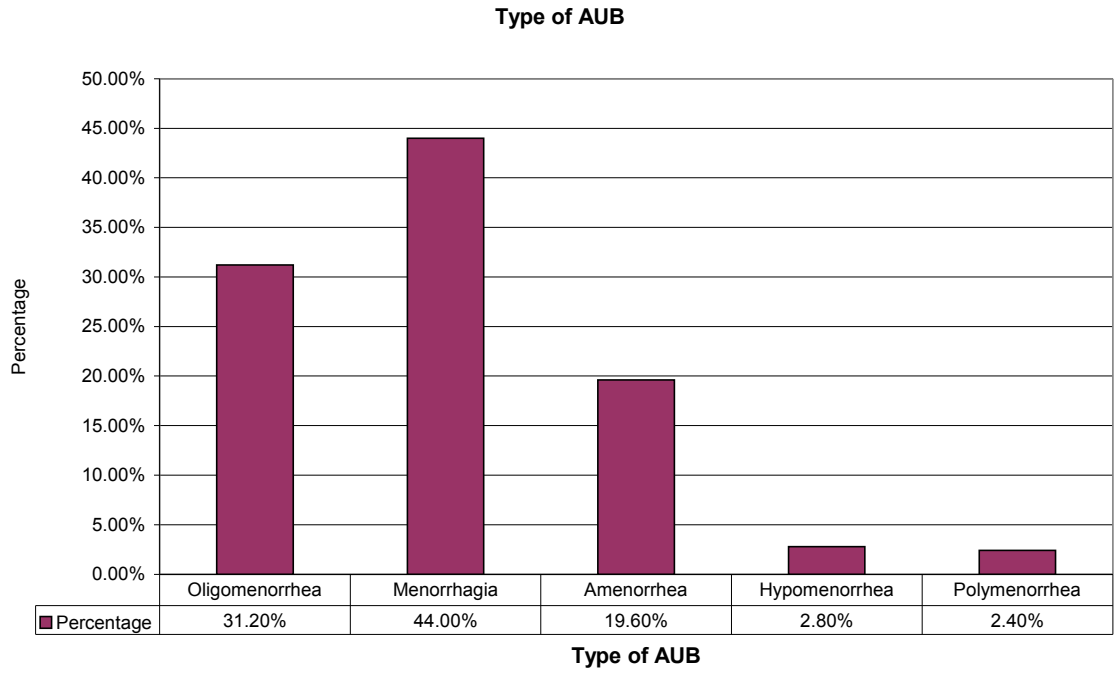


TABLE - 4

DURATION OF AUB

AUB Duration	Frequency	Percentage
1-3 months	97	38%
4-6 months	82	32.8%
7 months - 1 year	40	16.0%
1-3 years	23	9.2%
>3 years	2	0.8%
Since menarche	6	2.4%

Majority of the patients presented with AUB of 1-6 months duration

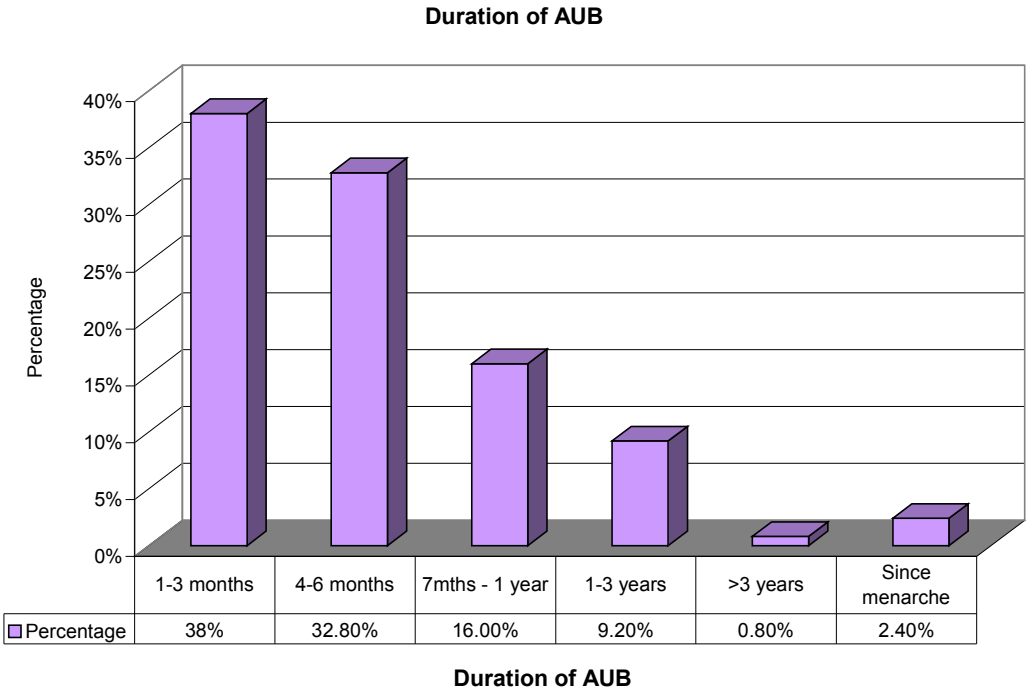


TABLE - 5

FREQUENCY OF AUB

No.of Episodes	Frequency	Percentage

First episode	193	77.2%
Second episode	28	11.2%
Third episode	16	6.4%
Fourth episode	6	2.4%
Fifth episode	4	1.6%
Sixth episode	3	1.2%

Majority of the patients presented at the first episode itself.

Only a minority reported after the fourth episode.

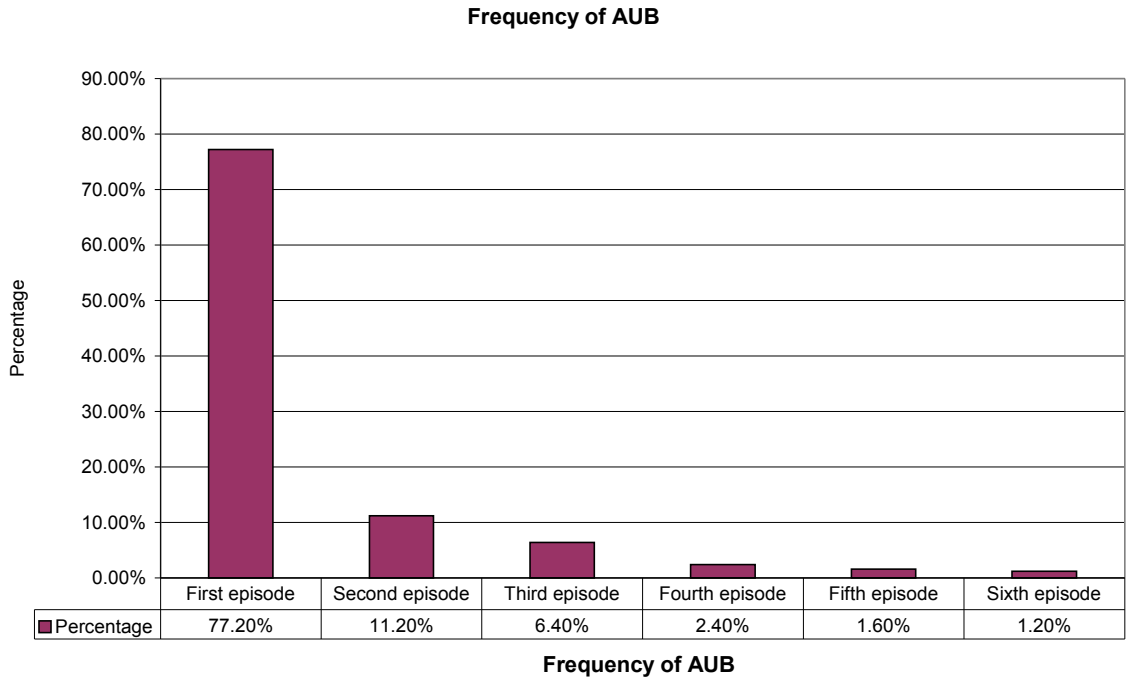


TABLE - 6

GENERAL EXAMINATION

General Examination	Number	Percentage

Normal	197	78.8%
Anaemia	44	17.6%
Thyromegaly	9	3.6%

21% of the patients had abnormal findings on examination. 80% were normal.

TABLE - 7

BMI - BODY MASS INDEX

BMI Range	Number	Percentage
< 18 (Lean)	6	2.4%
18-24 (Normal)	179	71.6%
25-29 (Overweight)	48	19.2%
30-34 (Obese)	12	4.8%
>34 (Morbid Obesity)	5	2.0%

6.8% of the patients were obese.

TABLE - 8

GYNAEC EXAMINATION

Size of the Uterus	Number	Percentage
Normal Size	216	86.4%
Bulky	34	13.6%

TABLE - 9

ULTRASONOGRAM

USG Findings	Number	Percentage

Not done	208	83.2%
Bulky Uterus	13	5.2%
Cystic ovaries	29	11.6%

TABLE - 10

FRACTIONAL CURETTAGE

Endometrial Histology	Number	Percentage
Not done	224	89.6%
Secretory	15	6.0%
Proliferative	11	4.4%

TABLE - 11

HAEMOGLOBIN ESTIMATION

Haemoglobin (gm%)	Number	Percentage
<9 gm%	40	16.0%
>9 gm%	172	68.8%
Not done	38	15.2%

TABLE - 12

SIGNS AND SYMPTOMS OF HYPOTHYROIDISM

Signs/symptoms	Number	Percentage
Nil	175	70%

Constipation	19	7.6%
Cold intolerance	1	0.4%
Voice change	11	4.4%
Weight gain	31	12.4%
Lethargy	12	4.8%
Palpitation	1	0.4%

70% of patients had no symptoms / signs of hypothyroidism. Weight gain was the most frequent symptom seen in 12.4% followed by constipation in 7.6%.

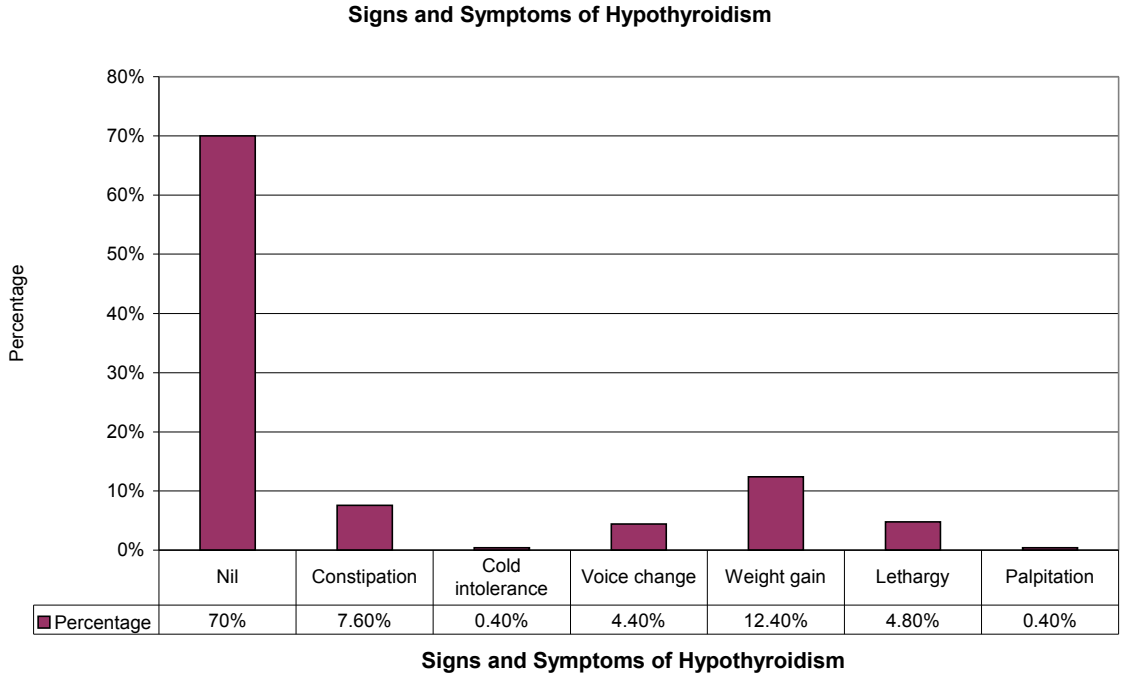


TABLE - 13

SIGNS AND SYMPTOMS OF HYPERTHYROIDISM

Signs / Symptom	Number	Percentage
Nil	132	52.8%

Heat intolerance	4	1.6%
Anxiety	12	4.8%
Weight Loss	22	8.8%
Fatigue	71	28.4%
Tremors	6	2.4%
Diarrhoea	3	1.2%

About 53% of the patients had no signs / symptoms of hyperthyroidism. The most common symptom was fatigue seen in 28.4%.

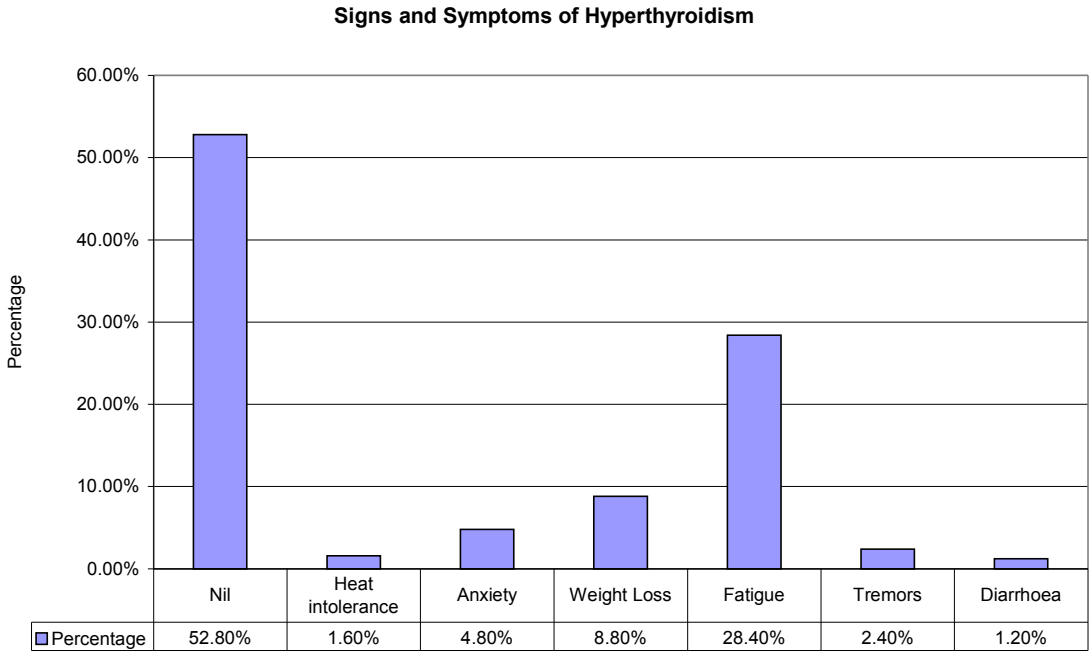


TABLE - 14

T_4 VALUES (N 4.8 -11.5 µg/dl)

T_4 (µg/dl)	Number	Percentage
<4.8	34	13.6%

4.8 - 11.5	199	79.6%
>11.5	17	6.8%

TABLE - 15

TSH VALUES (N 0.3 - 6.18 µIU/ml)

TSH (µIU/ml)	Number	Percentage
<0.3	23	9.2%
0.3 - 6.18	182	72.8%
>6.18	45	18.0%

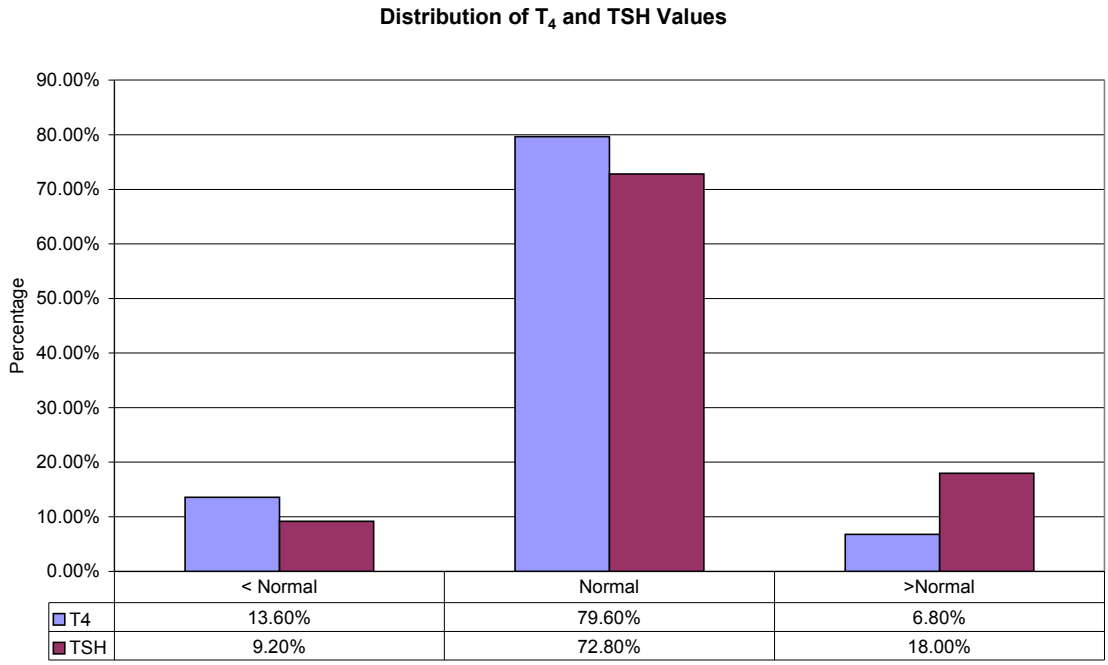


TABLE - 16

AMENORRHEA - AGE DISTRIBUTION

Age group (years)	Number	Percentage

18 - 24	7	14.28%
24 - 32	21	42.86%
32 - 40	18	36.73%
>40	3	6.12%

TABLE - 17

AMENORRHEA - PARITY DISTRIBUTION

Parity	Number	Percentage
Nullipara	8	16.3%
P_1L_1	10	20.41%
P_2L_2	24	48.98%
Multipara	7	14.28%

TABLE - 18

AMENORRHEA - T_4 VALUES (N 4.8 -11.5 µg/dl)

T_4 (µg/dl)	Number	Percentage
<4.8	9	18.37%

4.8 - 11.5	33	67.35%
>11.5	7	14.29%

TABLE - 19

AMENORRHEA - TSH VALUES (N 0.3 -6.18 µIU/ml)

TSH (µIU/ml)	Number	Percentage
<0.3	8	16.33%
0.3 - 6.18	31	63.27%
>6.18	10	20.41%

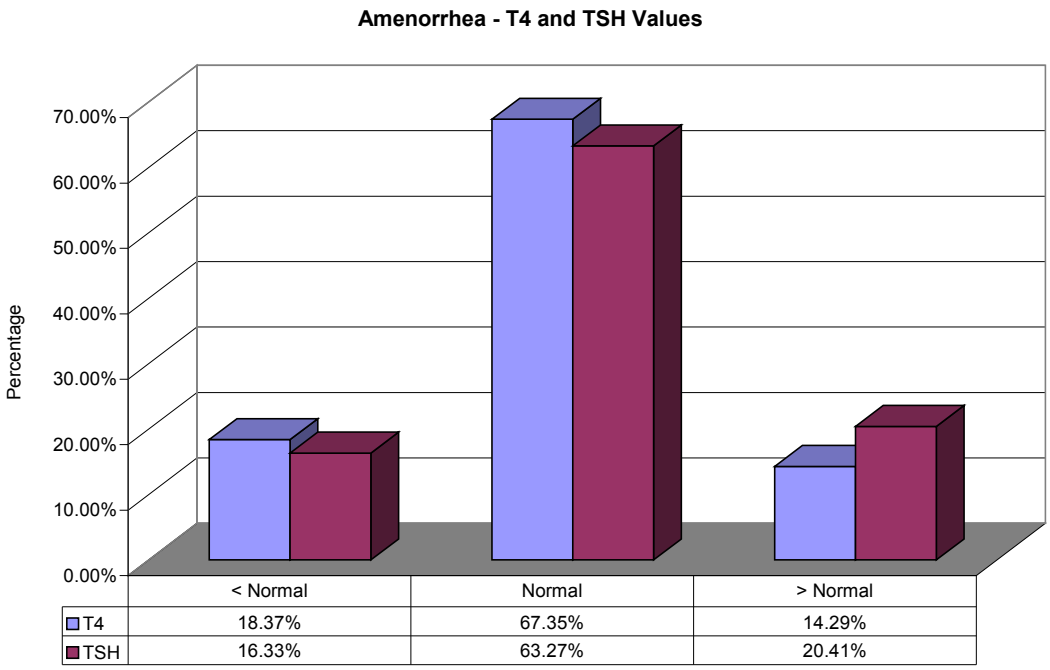


TABLE - 20

MENORRHAGIA - AGE DISTRIBUTION

Age group (years)	Number	Percentage
18 - 24	11	10%
24 - 32	86	78.18%
32 - 40	5	4.55%
> 40	8	7.27%

TABLE - 21

MENORRHAGIA - PARITY DISTRIBUTION

Parity	Number	Percentage
Nullipara	3	2.73%
P_1L_1	21	19.09%
P_2L_2	57	51.82%
Multipara	29	26.36%

TABLE - 22

MENORRHAGIA - T_4 VALUES (N 4.8 - 11.5 µg/dl)

T_4 (µg/dl)	Number	Percentage
<4.8	12	10.90%

4.8 - 11.5	98	89.09%
>11.5	-	-

TABLE - 23

MENORRHAGIA - TSH VALUES (N 0.3 -6.18 µIU/ml)

TSH (µIU/ml)	Number	Percentage
<0.3	-	-
0.3 - 6.18	88	80%
>6.18	22	20%

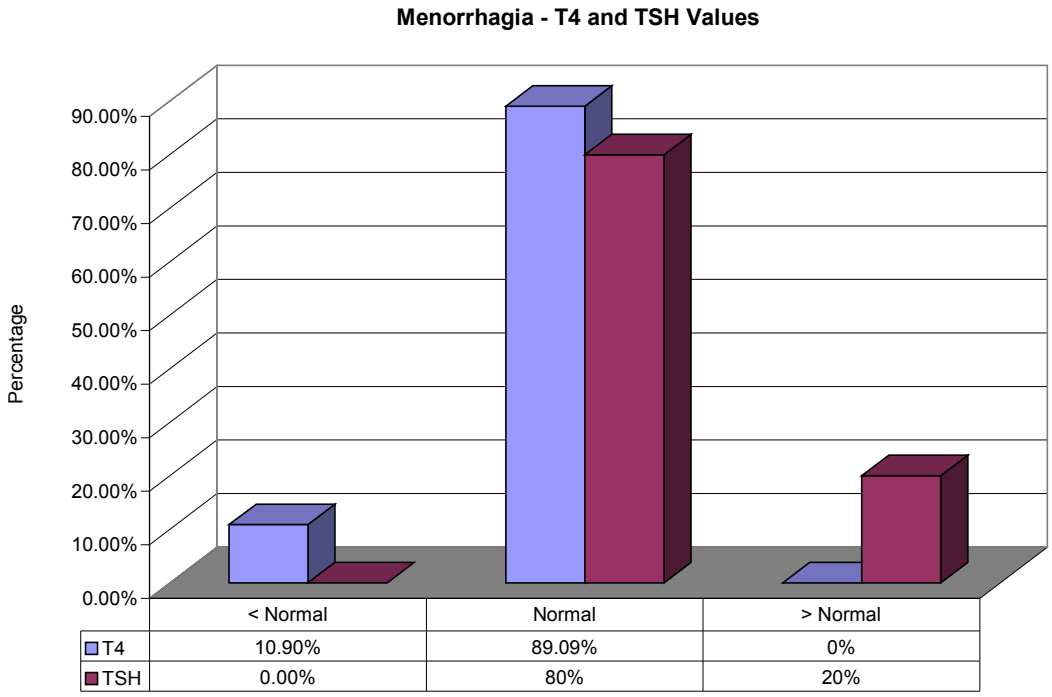


TABLE - 24

OLIGOMENORRHEA - AGE DISTRIBUTION

Age group (years)	Number	Percentage
18 - 24	12	15.38%
24 - 32	32	41.02%
32 - 40	24	30.76%
>40	10	12.18%

TABLE - 25

OLIGOMENORRHEA - PARITY DISTRIBUTION

Parity	Number	Percentage
Nullipara	15	19.3%
P_1L_1	26	33.33%
P_2L_2	34	43.58%
Multipara	3	3.84%

TABLE - 26

OLIGOMENORRHEA - T_4 VALUES (N 4.8 - 11.5 µg/dl)

T_4 (µg/dl)	Number	Percentage
<4.8	9	11.5%

4.8 - 11.5	56	71.8%
>11.5	13	16.66%

TABLE - 27

OLIGOMENORRHEA - TSH VALUES (N 0.3 -6.18 µIU/ml)

TSH (µIU/ml)	Number	Percentage
<0.3	11	14.1%
0.3 - 6.18	53	67.94%
>6.18	14	17.94%

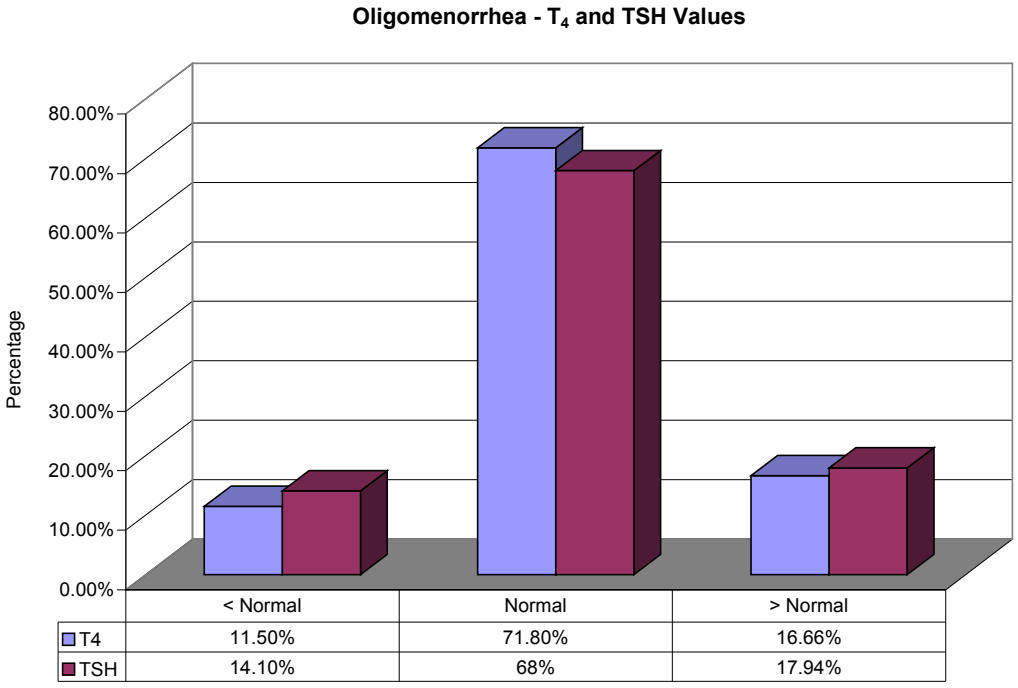


TABLE - 28

POLYMENORRHEA - AGE DISTRIBUTION

Age group (years)	Number	Percentage

18 - 24	2	33.33%
24 - 32	2	33.33%
32 - 40	-	-
>40	2	33.33%

TABLE - 29

POLYMENORRHEA - PARITY DISTRIBUTION

Parity	Number	Percentage
Nullipara	-	-
P_1L_1	2	33.33%
P_2L_2	3	50%
Multipara	1	16.66%

TABLE - 30

POLYMENORRHEA - T_4 VALUES (N 4.8 - 11.5 µg/dl)

T_4 (µg/dl)	Number	Percentage
<4.8	-	-
4.8 - 11.5	6	100%

>11.5	-	-

TABLE - 31

POLYMENORRHEA - TSH VALUES (N 0.3 -6.18 µIU/ml)

TSH (µIU/ml)	Number	Percentage
<0.3	-	-
0.3 - 6.18	5	83.33%
>6.18	1	16.66%

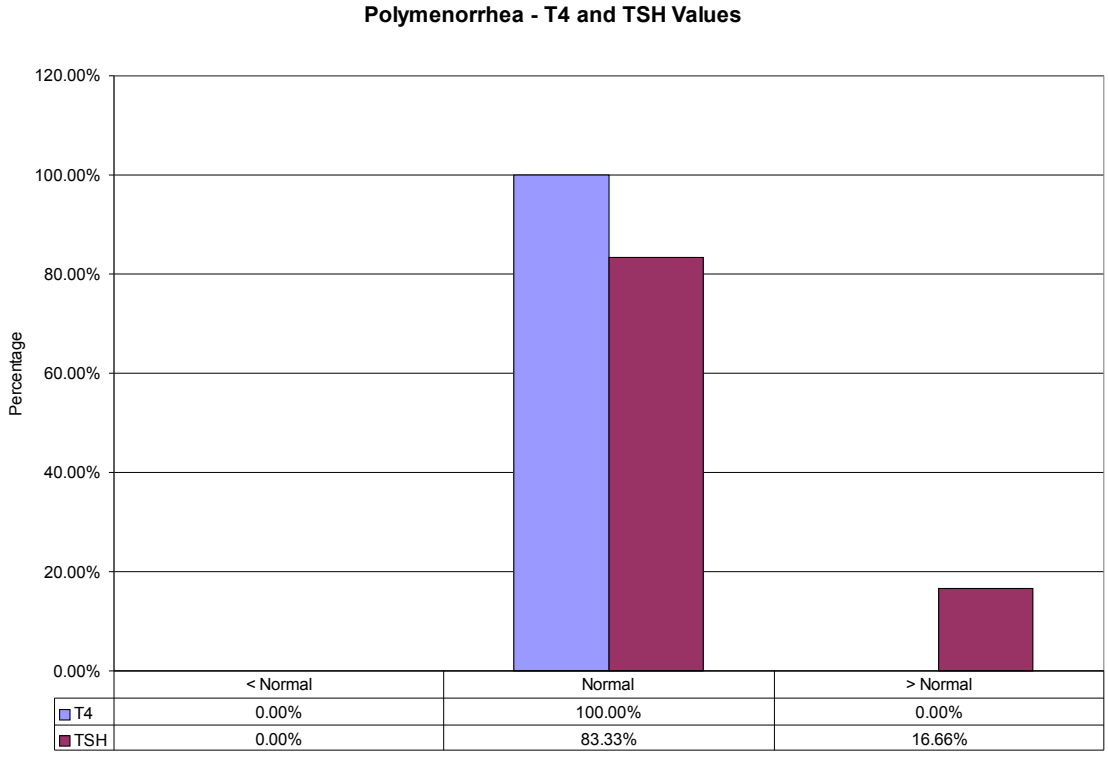


TABLE - 32

STUDENT 't' TEST WITH 5% LEVEL OF SIGNIFICANCE

Sl.No.	Variable	Chi Square (χ^2)	P Value (95% confidence interval)
1.	Age	4.73	0.019 Significant
2.	Parity	1.86	0.60 Not Significant
3.	Type of AUB	7.64	0.10 Not Significant

4.	Duration of AUB	12.96	0.02 Significant
5.	Number of episodes	10.76	0.3 Significant
6.	General Examination	15.82	0.001 Significant
7.	Body Mass Index	18.65	0.001 Significant
8.	Gynaec Examination	0.63	0.24 Not Significant
9.	USG	1.40	0.49 Not Significant
10.	Haemoglobin	0.40	0.53 Not Significant
11.	T_4	4.03	0.05 Significant
12.	TSH	4.13	0.03 Significant

TABLE -33

T_4 vs TSH AS A SCREENING TEST

Sensitivity	72% (60 - 82%)
Specificity	100% (98 - 100%)
Positive Predictive Value	100% (92 - 100%)
Negative Predictive Value	91% (85 - 94%)

DISCUSSION

AUB is a benign yet debilitating disease with a strong association with thyroid disorders. Our study highlights the association between AUB and thyroid dysfunction by measurement of T_4 and TSH in the fasting state in women with AUB.

Hypothyroidism is observed in 8.8% of women with menorrhagia, and 4.0% of women with amenorrhea. Hyperthyroidism is seen in 5.6% of women with oligomenorrhea. The overall incidence of thyroid dysfunction is 20.4%. This correlates with the study by Wilansky et al, 1992.

Study	Incidence of thyroid disorders
Prentice et al, 1999	36%
Wilansky et al, 1992	22%
Present study	20.4%

Some patients have a normal serum TSH despite low T_3 and T_4. This is explained by a downward resetting of the threshold for TSH inhibition TSH setpoint for a particular serum T_3, T_4 increases with age and is also altered by personal and familial character. TSH values tend to change more rapidly because the half life of TSH is much shorter than T_3 and T_4. This should be considered with regard to abnormal relationships between T_3, T_4 and TSH. There are some variations which should be given due consideration before interpreting the results.

1) T_4-Methodology, pregnancy

2) TSH - diurnal variation, pulsatile secretion.

Alteration in the relationship between T_4 and TSH can be caused by alternate thyroid stimulating hormones like TSH isoforms, chorionic gonadotrophins, and TSH receptor stimulating antibody. It can be caused by hormones and drugs like glucocorticoids, severe non-thyroidal illness, recent thyrotoxicosis and long standing hypothyroidism. The incidence of thyroid dysfunction in the reproductive age group is 1-2%. It is 10 times more common in women than in men. The incidence of thyroid dysfunction in a population with AUB is 20.4% according to our study and hence selective screening of this population would result in a higher yield.

A major benefit of routine testing is the earlier detection of unsuspected overt thyrotoxicosis or subclinical hypothyroidism or hyperthyroidism. Most clinicians advocate treatment of women with elevated TSH levels in view of risk of hypothyroidism developing subsequently.

The ACOG has recommended screening with sensitive TSH-assay in asymptomatic women over the age of 40 years. TSH assay meets the WHO criteria for a screening test.

(1) The condition should pose an important health problem.

(2) Natural history of the disease should be well understood.

(3) There should be a recognisable early stage.

(4) Treatment of the disease at an early stage should be of more benefit than treatment started at a later stage.

(5) There should be a suitable test.

(6) The test should be acceptable to the population.

(7) There should be adequate facilities for treatment of the abnormality detected.

(8) It should be cost effective.

(9) The chances of physical and psychological harm to those screened should be less than the benefit.

The TSH assay can also be used as a management and prognostic tool besides its use in diagnosis and screening.

SUMMARY

The present study is a cross-sectional study of 250 women with abnormal uterine bleeding in the reproductive age group undertaken in a tertiary referral hospital over a period of 8 months. It was done to ascertain the possibility of a correlation between subclinical thyroid dysfunction and AUB.

The history was elicited according to the proforma. Anthropometric measurement were taken and a detailed examination was done. T_4 and TSH levels were evaluated in the fasting rate and the results interpreted.

1) The study showed a significant correlation (p= 0.019, significant) between increasing age and thyroid dysfunction.

2) There was a significant correlation with the duration of AUB (p=0.02) and the number of episodes (p=0.03).

3) However there was no correlation with parity or the type of AUB.

4) The general examination and body mass index showed a significant correlation (p=0.001).

5) The USG and haemoglobin estimation did not show a significant correlation.

6) TSH is a good screening test with a sensitivity of 72% and specificity of 100%. The positive and negative predictive value were 100% and 91% respectively.

7) The findings of our study can be summarised as follows :

Incidence of hypothyroidism	13.6%
Incidence of hyperthyroidism	6.8%

In the different types of AUB:

a. Oligomenorrhea	hyperthyroidism	5.6%
	hypothyroidism	4.4 %
b. Amenorrhea	hyperthyroidism	3.2%
	hypothyroidism	4.0 %
c. Menorrhagia	hyperthyroidism	—
	hypothyroidism	8.8 %
d. Polymenorrhea	hyperthyroidism	—
	hypothyroidism	0.4 %

The incidence of thyroid disorders in polymenorrhea is low due to the higher incidence of PID in this group of patients(exclusion criterion).

CONCLUSION

It may be concluded from the present study that there is a significant association between thyroid disorders and AUB. The high incidence of thyroid disorders in women with AUB, particularly if the 7-10% of subclinical hypothyroidism is included, justifies the cost of screening in this selective population. The risk of progression to overt hypothyroidism (about 5% per year) in patients with subclinical disease and the cost-benefit ratio also emphasise the need for selective screening.

Early detection of subclinical disease by selective screening facilitates appropriate therapy early in the course of the disease.

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PROFORMA

Name Age Address

Sex Parity

Sterilisation

H/O

Menorrhagia ☐

Oligomennorrhea ☐

Amenorrhea ☐

Polymenorrhea ☐

Others ☐

O/E

General Condition

Anaemia

Thyromegaly

BMI

P/A

S/E

P/V

H/O S/S Hyperthyroidism

_____

_____

_____

H/O S/S Hypothyroidism

_____

_____

_____

Thyroid Function tests

T_4

TSH

Inference

Other Investigations

Hb in gm/dl

USG

Fractional Curettage

ABBREVIATIONS

AUB	-	Abnormal Uterine Bleeding
T_4	-	Thyroxine
T_3	-	Tri-iodothyronine
TSH	-	Thyroid Stimulating Hormone
TRH	-	Thyrotropin Releasing Hormone
LH	-	Luteinising Hormone
FSH	-	Follicle Stimulating Hormone
hCG	-	human Chorionic Gonadotrophin
TR	-	Thyroid hormone Receptor
RXR	-	Retinoid X Receptor
RT_3	-	Reverse T_3
TBG	-	Thyroid Binding Globulin
SHBG	-	Sex Hormone Binding Globulin
FT_4	-	Free Thyroxine
TT_4	-	Total Thyroxine
GnRH	-	Gonadotrophin Releasing Hormone
Anti TPO	-	Anti Thyroid Peroxidase
Anti TG	-	Anti Thyroglobulin
BMI	-	Body Mass Index
PID	-	Pelvic Inflammatory Disease
IUCD	-	Intrauterine Contraceptive Device
IRMA	-	Immuno Radiometric Assay
BRIT	-	Board of Radiation and Isotope Technology
ACOG	-	American College of Obstetrics and Gynaecology