“STUDY OF THYROID DYSFUNCTION IN PATIENTS WITH DYSFUNCTIONAL UTERINE BLEEDING”

BY

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IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF

MASTER OF SURGERY IN

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ABBREVATIONS

DUB : Dysfunctional Uterine Bleeding

OPD : Out Patient Department

T_3 : Triiodithyronine

T_4 : Thyroxine

TSH : Thyroid Stimulating Hormone

TPO-Ab :Thyroid Per Oxidase Antibody

TgAb :Thyroglobulin Antibody

TBG : Thyroxin Binding Globulin

TRH : Thyrotrophin Releasing Hormone

MIT : Monoiodothyronine

DIT : Di iodothyronin

RIA : Radio Immuno Assay

MPH : Metropathia Hemorrhagica

TFT : Thyroid Function Tests

TDF : Thyroid Dysfunction

USG : ultrasound

Vs : versus

Y : yes

N : no

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ABSTRACT

TITLE-STUDY OF THYROID DYSFUNCTION IN PATIENTS WITH PROVISIONAL DIAGNOSIS DYSFUNCTIONAL UTERINE BLEEDING

AIM AND OBJECTIVES:

DUB accounts for 10% of all gynaecology related complaints. The aim of this study is to evaluate the thyroid function in patients having abnormal menstrual bleeding from puberty to premenopausal age groups which is interesting and justifiable and will help in further management of DUB and also know the prevalence of thyroid dysfunction in patients provisionally diagnosed as DUB. The objectives are to evaluate and detect the thyroid dysfunction in patients with dysfunctional uterine bleeding in reproductive age group and to refer positive cases to the physician for further treatment of thyroid disorder.

MATERIALS AND METHODS:

This study is carried out in the department of Obstetrics and Gynecology, Sri B M Patil Medical college on 140 women who were clinically given the provisional diagnosis of DUB. All these patients were subjected to routine investigations and T3, T4 , TSH & TPOAb estimation and were grouped as euthyroid, subclinical hypothyroid, hypothyroid or hyperthyroid.

RESULTS:

Out of the 140 patients taken into study 17 had thyroid disorders, out of which subclinical hypothyroidism was most prevalent accounting for 10 cases, 5 cases of hypothyroidism and 2 cases of hyperthyroidism.

CONCLUSION:

There is a high prevalence of thyroid disorders in cases which are clinically diagnosed as DUB. Hence the biochemical evaluation of T3, T4, TSH, TPOAb is extremely important and valuable in detecting these patients. Unnecessary surgery was avoided in 12% of patients and they were treated medically which was more accurate and cost effective. Hence thyroid function evaluation should be made mandatory in cases of DUB to detect thyroid dysfunction.

KEY WORDS: Dysfunction Uterine Bleeding (DUB), Subclinical Hypothyroidism, TPOAb.

INTRODUCTION

Dysfunctional uterine bleeding is an abnormal bleeding from the uterus in the absence of any palpable pelvic pathology and demonstrable extragenital cause.[1] DUB accounts for 10% of the gynaecology related complaints. Thyroid dysfunction is also marked by large number of menstrual irregularities.

Both hypo as well as hyperthyroidism are associated with delayed onset of puberty, anovulatory cycles and abnormally high foetal wastage.[2] Clinical experiences show increased menstrual flow to be the most common reproductive system manifestation of hypothyroidism. Although the occurrence of menstrual disturbances in hypothyroid woman has been documented, the number of hypothyroid patients, originally requiring treatment for menorrhagia has not been carefully elicitated.[3] Majority of the cases of subclinical hypothyroidism easily pass unrecognized. The prevalence of subclinical hypothyroidism is as high as 9.5% in women.[4]

Danese MD et al recommend hypothyroidism is frequent enough to warrant consideration in most older woman, justifying screening even in asymptomatic older women.[5] Ely et al mentions state that any irregular bleeding in non pregnant patient and in non pregnant patients with menorrhagia TSH should be evaluated.[6]

The introduction of serum thyroxine (T3) , serum thyroid stimulating hormone (TSH) & thyroid peroxidase antibody radioimmunoassays has increased the sensitivity and specificity of thyroid function testing. The serum TSH assay has been shown to be a

sensitive indicator of diminished thyroid functional reserve, since TSH levels become elevated before circulating serum thyroxine levels fall below the normal range.[7]

Presence of TPO-Ab is a pathologic finding. It is an early risk marker for elevated TSH and ensuing hypothyroidism. Approximately 5 percent per year will develop clinical hypothyroidism in patients with elevated TPO-Ab and elevated TSH.[17]

Hence this study is to evaluate the thyroid function in patients having menstrual disturbances from puberty to premenopausal age groups which will be interesting and justifiable and will help in further management of DUB and also know the prevalence of hypothyroidism in patients provisionally diagnosed as DUB.

OBJECTIVE OF THE STUDY

PRIMARY OBJECTIVE

To evaluate and detect the thyroid dysfunction in patients with dysfunctional uterine Bleeding.

SECONDARY OBJECTIVE

To treat thyroid dysfunction medically and there by avoid surgery

REVIEW OF LITERATURE

Rosalind Pitt Rivers and WR Trotter, 1964 in their earlier publication 'The thyroid Gland' stated that in thyroid deficiency the effect related to ovarian function that is most frequently observed is a change in the rhythm of the oestrus cycle, generally resulting in lengthening or irregularity.

'Chu' found a marked increase in the number of unruptured follicle and a decrease in the number of ovulations in the ovaries of the rabbits from which thyroid was removed surgically. He attributed these changes to an increase in the secretion of FSH and a decrease in that of LH by the pituitary.[8]

Scott and Mussey, 1964, reported incidence of subjective menorrhagia in myxodema varies from 32 to 80% and menorrhagia may not infrequently be the presenting complaint. Hyperthyroidism in contrast is associated with oligomenorrhoea and amenorrhoea which are in proportion to the severity of the thyrotoxicosis. The menorrhagia associated with hypothyroidism responds promptly to thyroid replacement, often in doses insufficient to correct the other manifestations of the condition, suggesting that thyroxine does in some way have a direct effect on the spiral arterioles and on haemostasis at menstruation.[9]

The study on the plasma levels of estrogen measured daily by radioimmunoassay for 28 consecutive days in 12 healthy euthyroid women and 15 thyrotoxic women 10 with

hypomenorrhoea and 5 with amenorrhoea, showed, that the menstrual disturbance which occurs in thyrotoxicosis is associated with raised circulating oestrogen levels.[10]

A correlation of low platelet adhesiveness and other hemostatic abnormalities, in hypothyroidism was shown in another study. This platelet dysfunction in combination with other factors can lead to menorrhagia in hypothyroidism.[11]

Sheldon S. Stoffer, 1982 presented case reports where the apparent relationship between menstrual disturbance and minimal thyroid insufficiency was documented by patients dramatic response to treatment with levothyroxine. In 2 of these cases levothyroxine therapy was discontinued and menstrual abnormality returned. The mechanism of menstrual dysfunction observed in patients with minimal thyroid insufficiency is not clear.[12]

Ivor M.D. Jackson, 1982 stated that thyrotropin releasing hormone was equally effective in stimulating prolactin secretion from the normal pituitary gland although the importance of this hypothalamic releasing factor in the regulation of the pituitary thyroid axis in human beings have to be studied further for understanding physiologic importance.[13]

In a study of 70 cases of puberty menorrhagia, it was seen that 5 cases had hypothyroidism (7.15%) and 3 out of these 5 hypothyroid patients had no other disturbance clinically suggestive of hypothyroidism. Hypothyroidism was the second

common cause of excessive puberty bleeding. Adolescents with hypothyrodism tend to have milder symptoms than older patients.

The cause of excessive bleeding in hypothyroidism remains in the realm of speculation..[14]

When 67 apparently euthyroid menorrhagic women were evaluated with a thyrotropin releasing hormone test, 15 (22%) out of 67 showed “mild primary hypothyroidism” characterized by a elevation of basal TSH level (5.9 MU/L), lowering of serum thyroxine levels (85 nmol/l) and exaggerated response of serum TSH and thyroxine to administration of thyrotrophin releasing hormone. The terms “early” and “potential “ hypothyroidism describe the preliminary phase of hypothyroidism. During the follow up, menorrhagia disappeared within 3 to 6 months and didnot reappear in 1 to 3 years in all patients with early hypothyroidism to whom Lthyroxine was given along with improvement in thyroid profile without change in triiodothyroxine levels.3

I.Ross McDougall, 1992 stated that “there is a clinical impression that hypothyroid patients have a bleeding tendency”. However this is seldom a clinical problem. Several case reports describes hypothyroid patients with a significant bleeding diathesis in whom the underlying cause is not completely defined. The usual finding is similar to Von Willebrand’s 9 disease with low concentration of factor VIII and an inhibitor of coagulation”. Treatment with thyroxine correctsthe problem.[15]

In a study of 189 hypothyroid women to find out their menstrual pattern and fertility status. As many as 91 patients (71.09%) had subclinical hypothyroidism; 46.87% had normal menstrual pattern. Menstrual aberrations included mainly, oligomenorrhoea, hypomenorrhoea, menorrhagiaand secondary amenorrhoea. Oligomenorrhoea was the commonest menstrual abnormality found mainly in early age group women. Menorrhagia was commoner in later age group.21 In this study author has commented that " as majority of cases are subclinical, it is essential to evaluate thyroid function in all women with intractable menstrual disorders, infertility and recurrent pregnancy loss.[16]

Leon Speroff 2010, explains menstrual irregularities and bleeding problems being common in hypothyroid women. Amenorrhoea can be a consequence of hypothyroidism either with TRH induced increase in prolactin or with normal prolactin levels. He explained the involvement of sex hormone binding globulin (SHBG). SHBG is a glycoprotein synthesised in liver and contains a single binding site for androgens and oestrogens. Oestrogen and thyroxine are stimulatory for its production. Free oestrodiol levels are increased because of significant decrease in SHBG. The total binding capacity of SHBG will thus influence the amount that is free and unbound. High levels of estrogen and sustained availability leads to prolonged period of amenorrhoea followed by acute, often profuse bleeds with excessive loss of blood.[17]

In a recent study conducted on 213 patients with DUB, menorrhagia as their chief menstrual abnormality hypothyroidism was detected in 28.17% of the cases proliferative endometrium was seen in majority of hypothyroid patients. 78% patients responded to medical line of treatment thereby avoiding hormones or surgical intervention. It was also noted that 5%patients were clinically euthyroid but demonstrated altered biochemical levels while 55% patients had symptoms/signs/both. Easy fatigability was the commonest symptom.

Menstrual pattern among hypothyroid patients[18]

Sl No.	Type	No. of Patients % (out of 60)
1	Menorrhagia	38(63.33%)
2	Polymenorrhagia	14(23.33%)
3	Metropathia	4(6.66%)
4	Metrorrhagia	4(6.66%)

According to some studies conducted by Wilansky DI et al., menorrhagia disappeared within 3 to 6 months and did not reappear in 1 to 3 years of follow up in all patients with early hypothyrodisim to whom L-thyroxine.[19]

In a study conducted by JV Joshi et al., it is found that only 31.8% of hypothyroid and 35.3% of hyperthyroid in women had normal menstruation pattern in contrast with 56.3% of Euthyroid and 87.8% of healthy controls ($p < 0.001$). It has been stated that menorrhagia is more common in hypothyroidism or myxoedema, while anovulation or oligomenorrhoea is more common in hyperthyroidism. The aim of the study was to determine the proportion of cases with thyroid disorders having menstrual irregularity. All the types of menstrual abnormalities were significantly more frequent in women with hypo and hyperthyroidism compared to control cases. More than 45% of cases with hypo / hyperthyroidism the menstrual abnormalities preceed the appearance of goiter or clinical symptoms and signs. Therefore they summerised that any type of menstrual disorders should be considered as a possible presenting symptoms of thyroid dysfunction and it may indicate sub clinical abnormality.[20]

According to studies conducted by Krassas GE et al.,TSH, T4, T3 & thyroid anti-bodies were measured by radioimmunoassay, while BMI was calculated from the ratio of body weight in kg to height in m^2.These data demonstrate that in hypo-thyroidism menstrual irregularities tend to be more frequent in severe hypothyroidism in comparison with mild cases.[21]

According to BMJ, 2000 letter, evidence supports association between hypothyroidism and menorrhagia.[22]

The possible advantages of treating sub clinical hypothyroidism generally include firstly, preventing the progression to overt hypothyroidism. Secondly thyroxine therapy may improve the serum lipid profile and there by potentially decreased the risk of death from cardiovascular causes. Finally treatment may reverse the symptoms of mild hypothyroidism, including psychiatric and cognitive abnormalities. Most agree that patients with serum TSH greater than 10mU/l should be treated with thyroxine. The AACE has recommended treatment in patients with TSH level between 5 and 10 mU/l. In conjunction with a goiter or positive antithyroid peroxidase antibodies or both and also in the presence of symptoms, if patients are antibody negative, then annual checkup of serum TSH is recommended with commencement of T4 once the serum TSH rises above 10 mU/l.[23]

According to Merck Manual Professional, Subclinical thyroid dysfunction is relatively common; it occurs in more than 15% of elderly women patients with serum TSH > 10 mU/L have a highly likelihood of progression to overt hypothyroidism. Patients should have annual measurement of serum TSH and free T4. Serum TSH is the most sensitive test for screening thyroid disorders.[24]

According to American family physician publication in 2004, literature once pregnancy and iatrogenic causes have been excluded, patients should be evaluated for disorders, particularly thyroid. Menstrual irregularities are associated with both hypothyroidism (23.4 percent of cases), hyperthyroidism (2.15 percent of cases).[25]

According to American Family Physician, 2005, subclinical hyperthyroidism appears to be associated with atrial fibrillation, reduction of bone density, cardiac dysfunction and progression to overt hyperthyroidism in patients.[26]

Studies show that prevalence of sub clinical hypothyroidism is 4% to 8% in the general population, and up to 15% to 18% in women who are over 60 years of age.[27]

Novak S 2011, mentions both hypothyroidism and hyperthyroidism can be associated with abnormal bleeding. With hypothyroidism, menstrual abnormalities, including menorrhagia are common. Hyperthyroidism can result in oligomenorrhoea and amenorrhoea and it can also lead to elevated levels of plasma oestrogen. Also coagulation abnormalities such as Von Willebrand's disease can have a variable clinical picture and may escape diagnosis until the reproductive years.[28]

Jeffcoates 2008, mentions, hypothyroidism tends to cause menorrhagia or polymenorrhoea these symptoms being present in 30-40% of cases. Thyroid function should be especially evaluated in cases of menorrhagia. Hypothyroidism and hyperthyroidism can both depress ovarian and menstrual function. The latter never causes amenorrhoea unless exophthalmos is present. When hyperthyroidism is associated with

amenorrhoea, it is necessary to recognize that it may be merely a manifestation of a pituitary fault which is also the cause of menstrual upset.

Hypothyroidism is associated with an increase in thyrotrophin releasing hormone which is turn may be associated with a raised prolactin level and hence amenorrhoea.[29]

In a study conducted by Kaur T et al., Out of 100 patients studied, 14 had hypothyroidism,one patient had hyperthyroidism and rest 85 were euthyroid. Of 14 hypothyroid patients, 9(64.3%) had menorrhagia, 3(21.4%) had oligomenorrhoea and one patient with hyperthyroidism was found to have hypermenorrhagia. Hypothyroid patients with TSH levels below 13.5μIU/ml had either menorrhagia or metrorrhagia, but as TSH rises upto 20μIU/ml ,oligomenorrhea was the cheif complaint. 9(64.3%) hypothyroid patients had proliferative endometrium, 3(21.4%) had endometrial hyperplasia and rest 2(14.3%) had secretory endometrium.[30]

In a study conducted by Sharma N, Sharma A; Fifty patients of DUB (Group-A) in reproductive age group presenting with menstrual irregularities like menorrhagia, oligomenorrhoea, amenorrhoea, hypomenorrhoea and polymenorrhoea were studied for thyroid profile and fifty thyroid patients were studied in endocrinology for menstrual patterns (Group-B). Out of 50 women (Group-A), hypothyroidism was detected in 11(22%) and hyperthyroidism in 7 (14%). In Group-B 56 % of hypothyroid patients had disturbed menstrual cycles with associated problems and 62 % of hyperthyroid patients were found to have disturbed menstrual cycles ranging from menorrhagia to oligomenorrhoea to amenorrhoea. Thyroid function tests must be ordered in women presenting with DUB, to avoid unnecessary hormonal treatment and surgery in such

patients.[31]

Sinclair D described Thyroid peroxidase (TPO), originally described as thyroid microsomal antigen, is present on the apical surface of thyroid follicular cells and is the antigen involved in cell-mediated cytotoxicity. Multiple B-cell-reactive epitopes exist, each giving rise to different antibodies. The aetiology and mechanics of the autoimmune cellular and antibody responses involves a combination of human leucocyte antigen (HLA) linkage, genetics and environmental factors to determine the initial and subsequent stages of the development of autoimmune thyroid disease. Depending on the antibody, a combination of enzyme-linked immunosorbent assay for TPO and thyroglobulin and bioassays and/or radioimmunoassay for TSH receptor antibodies are used to estimate their concentrations. The review also itemizes the circumstances in which it might be useful to measure each antibody (i.e. the use of TPO antibodies in investigation of goitre, diagnosis of Graves' and Hashimoto's disease and the prediction of risk of developing hypothyroidism during subclinical thyroid disease; TSH receptor antibodies in maternal and neonatal hyperthyroidism and thyroglobulin antibodies in the monitoring and treatment of thyroid carcinoma[32]

Engler H states the identification of the thyroid peroxidase (TPO) as the main antigen of the thyroid microsomal fraction has enabled the development of a sensitive and specific assay for detection of the corresponding autoantibodies. Clearly elevated anti-TPO values (anti-TPO > 500 units/ml) were found in 59% of patients with thyroiditis but in none of the controls or the patients with non-thyroidal illness. The mean anti-TPO levels in these two control groups were 26 +/- 31 units/ml (mean +/- S.D.) and 39 +/- 34 units/ml, respectively. The highest frequency of positive results (88%) was obtained in

patients with auto-immune hypothyroidism (clinical diagnosis: Hashimoto's thyroiditis) followed by patients with Graves' disease (53%). With a cut-off point of 200 units/ml, a sensitivity of 96% was obtained for Hashimoto's thyroiditis and of 59% for Graves' disease with a specificity of 100% (50 cases).[33]

Hollowell et al stated TPOAb were significantly associated with hypo or hyperthyroidism, but TgAb were not. TgAb alone in the absence of TPOAb is not significantly associated with thyroid disease.[34]

In a study conducted by Elio Roti et al they have evaluated the prevalance of AbTPO in elderly subjects and compared the results obtained with other methods to detect the presence of serum anti-thyroid antibodies. They observed AbTPO and AbM (RIA) tests were positive in -40% of the subjects with increased serum TSH concentrations, whereas the PH tests were positive only in 8%. This suggests that the AbTPO (RIA) and AbM (RIA) tests may more accurately diagnose the pathogenesis of thyroid dysfunction than the PH tests.[35]

Embryology of thyroid gland[36]

The tissue bud that ultimately becomes the thyroid gland arises initially as a midline diverticulum in the floor of the pharynx. This tissue originates in the primitive alimentary tract and consists of cells of endodermal origin. The main portion of this cellular structure descends into the neck and develops into a bilobar solid organ.

A normally developed adult thyroid is a bilobed structure that lies next to the thyroid cartilage in a position anterior and lateral to the junction of the larynx and trachea. In thisposition the thyroid encircles about 75% of the diameter of the junction of the larynx and the upper part of the trachea. The two lateral lobes are joined at the midline by an isthmus, whose superior edge is situated at or just below the cricoid cartilage.

The pyramidal lobe represents the most distal portion of the thyroglossal duct and in an adult may be a prominent structure that can extend from the midline of the isthmus as far cephalad as the hyoid bone.

Blood Supply

The arterial supply to the thyroid gland consists of four main arteries, two superior and two inferior. Three pairs of venous systems drain the thyroid.

PHYSIOLOGY OF THE THYROID GLAND

The thyroid gland weighs 10 to 20 g in normal adults and is responsible for the production of two families of metabolic hormones: the thyroid hormones thyroxine (T4) and triiodothyronine (T3) and the calcium-regulating hormone calcitonin. The spherical thyroid follicular unit is the important site of thyroid hormone production. The thyroid follicle is made up of a single layer of cuboidal follicular cells that encompass a central depository of colloid filled mostly with thyroglobulin (Tg), the protein within which T4 and T3 are synthesized and stored. Each follicle is surrounded by a rich network of

capillaries that interdigitate among the multiple follicular units contained within normal thyroid matrix.[37]

Iodine Is Essential For Normal Thyroid Function

It can be efficiently absorbed from the gastrointestinal tract in the form of inorganic iodide and rapidly enters the extracellular iodide pool. The thyroid gland is responsible for storing 90% of total body iodide at any given time, with less than 10% existing in the extracellular pool. The extracellular pool consists of freshly absorbed iodide, as well as the total derived from the breakdown of previously formed thyroid hormone. Within the thyroid, iodide is stored either as preformed thyroid hormone or as iodinated amino acids.

Iodide is transported from the extracellular space into the follicular cells against a chemical and electrical gradient. The transporter is an intrinsic transmembrane protein located in the basolateral membrane of the thyroid follicular cells.[38]

Once inside the cells, iodide rapidly diffuses to the apical surface, where it is quickly moved to exocytic vesicles. Here it is rapidly oxidized and bound to Tg. Transport of iodide into follicular cells is regulated by thyroid-stimulating hormone (TSH) from the pituitary gland, as well as by the follicular content of iodide.

C cells, derived from the neural crest, migrate into the thyroid during embryologic development. These cells rest in a parafollicular position, predominantly in the upper lobe of each thyroid. C cells are responsible for production of the hormone calcitonin, which has important regulatory properties on calcium metabolism.

Thyroid Hormone Synthesis

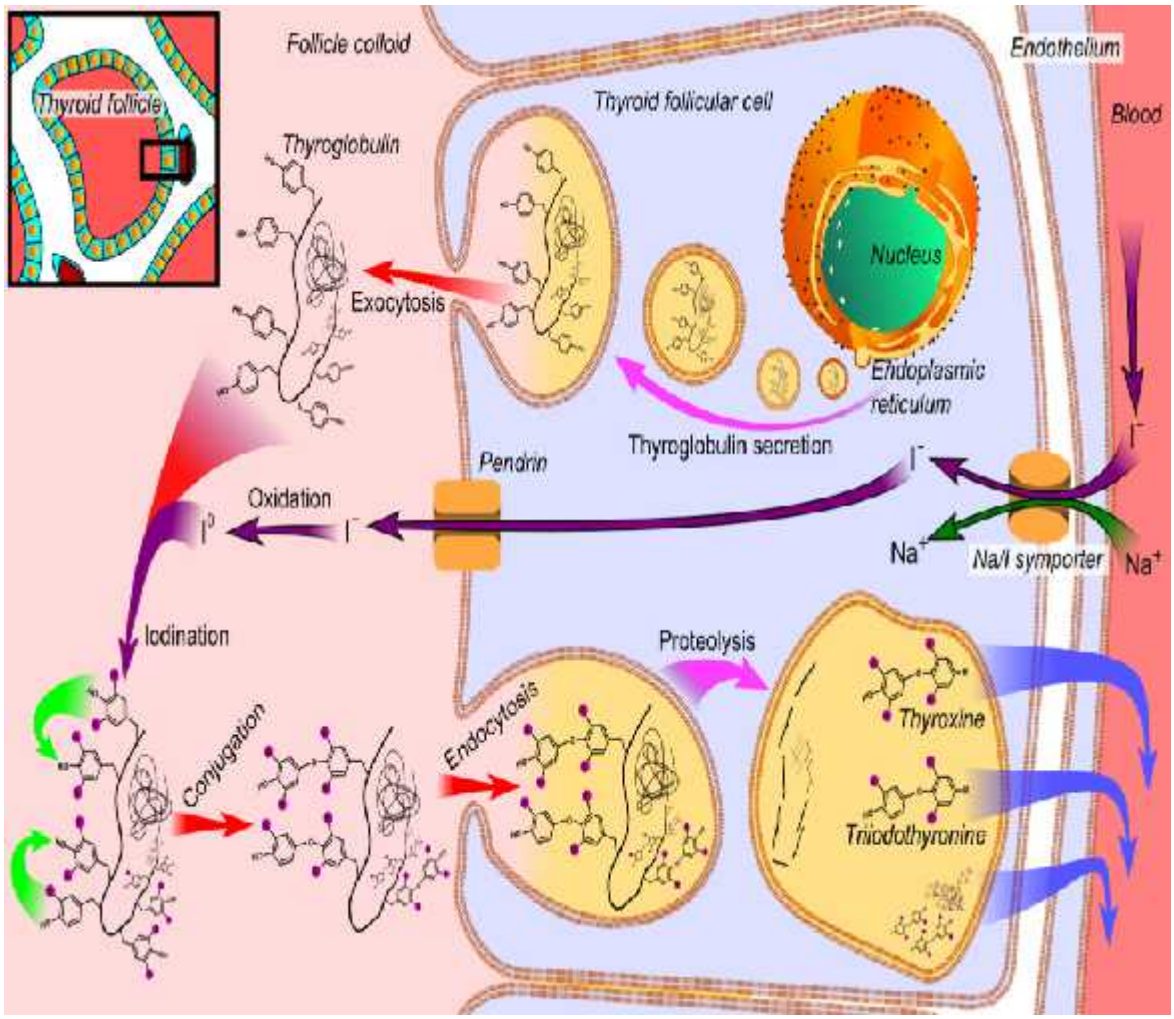
Once organic iodide is efficiently oxidized and bound, it couples to Tg with tyrosine moieties to form iodotyrosines in either a single conformation (monoiodotyrosine [MIT]) or a coupled conformation (diiodotyrosine [DIT]). The formation of DIT and MIT is dependent on an important intracellular catalytic agent, thyroid peroxidase, which has been well characterized and is an integral part of the initial process of organification and storage of inorganic iodide. This enzyme is localized to the apical portion of the follicular cell, where it reacts at the cellcolloid interface.

MIT and DIT are biologically inert. Coupling of these two residues gives rise to the two biologically active thyroid hormones T4 and T3. T4 is formed by coupling of two molecules of DIT, whereas T3 is formed by coupling of a molecule of MIT with a molecule of DIT. In normal circumstances, formation of T4 is the major pathway. Both T3 and T4 are bound to Tg and stored within the colloid in the center of the follicular unit, which allows quicker secretion of the hormones than if they had to be synthesized. This rapid and metabolically active process results in the storage of about 2 weeks' worth of thyroid hormone within the organism under normal circumstances.[39]

The majority of thyroid hormone released from the thyroid gland is T4, which is deiodinated in peripheral extrathyroidal tissues and converted to T3.

Release of T4 and T3 is regulated by the apical membrane of the follicular cell via lysosomal hydrolysis of the colloid that contains the Tg-bound hormones. The apical membrane of the thyroid cell forms multiple pseudopodia and incorporates Tg into small vesicles, which are then brought within the cell apparatus. Within the vesicles, lysosomal

hydrolysis results in reduction of the disulfide bonds, and both T3 and T4 are then free to pass through the basement membrane and be absorbed into the circulation, where more than 99% of each of the hormones is bound to serum proteins.[40]



REGULATION OF THYROID HORMONE SYNTHESIS

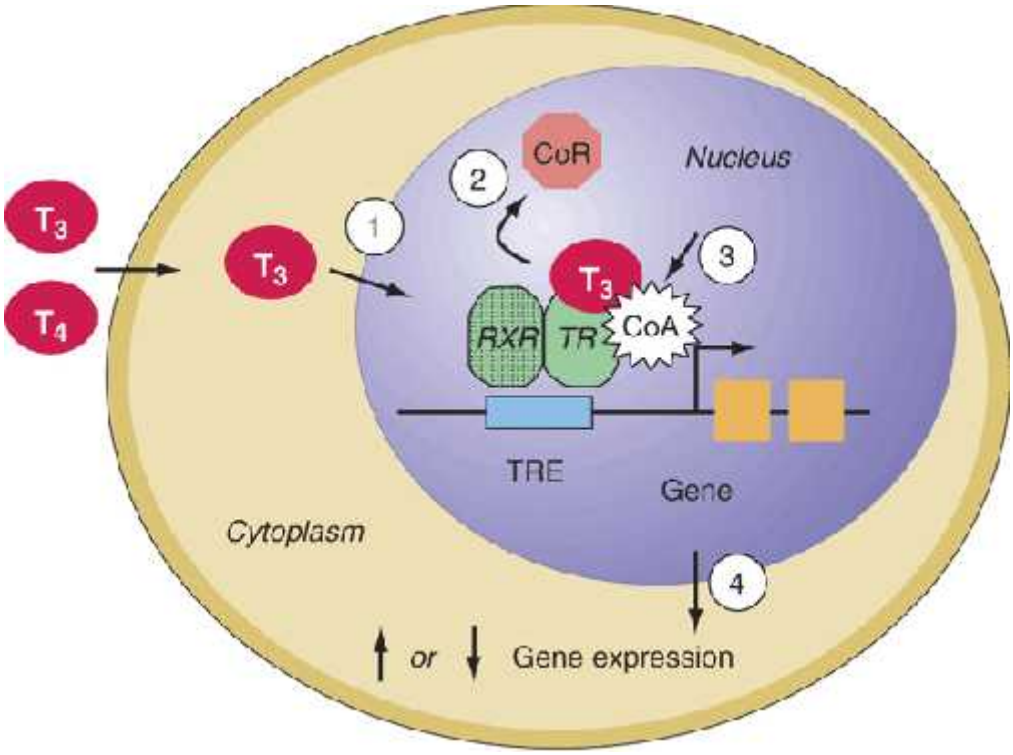


Fig 2: MECHANISM OF THYROID HORMONE RECEPTOR ACTION

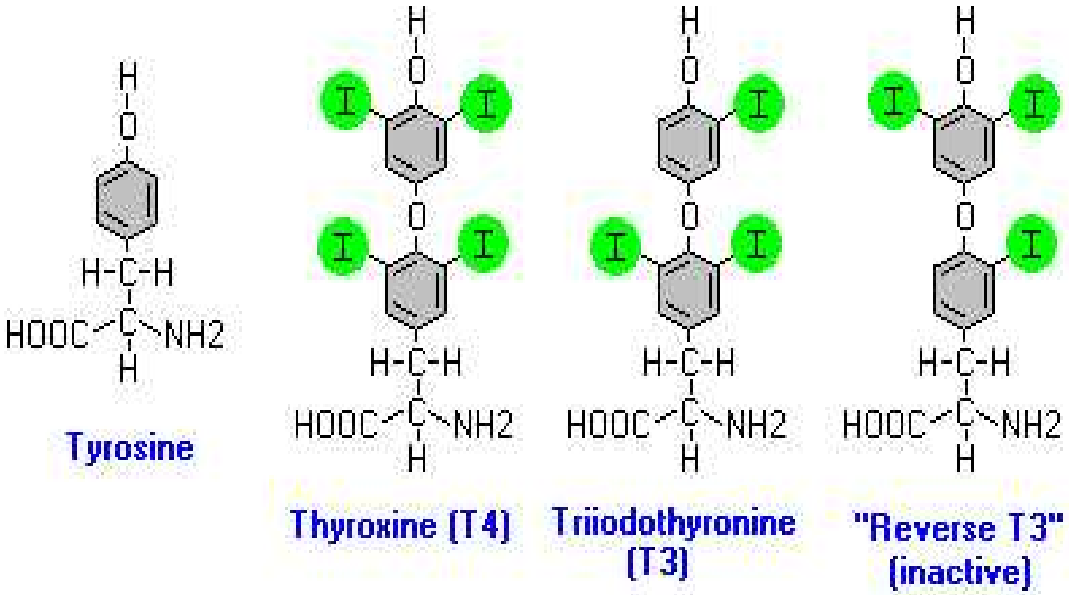
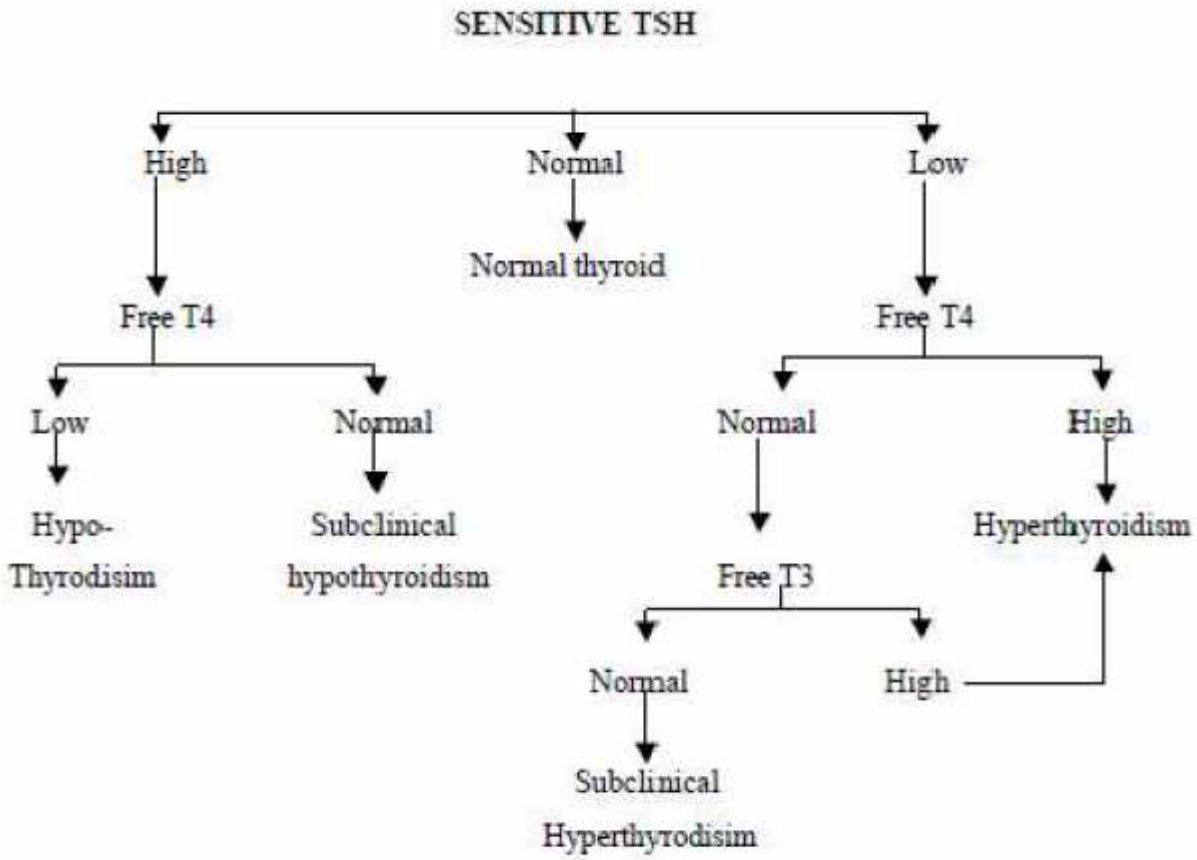


Fig 3: MOLECULAR STRUCTURE

Fig 4: VARIATIONS OF TSH,T3,T4



Regulation of Thyroid Hormone Secretion [36]

Triiodothyronine and Thyroxine

The hypothalamic-pituitary-thyroid axis regulates thyroid hormone production and release in a classic endocrine feedback system. The major regulator of thyroid gland activity is the glycoprotein TSH, which is a major growth factor for the thyroid. TSH stimulates thyroid cell growth and differentiation, as well as iodine uptake and organification and release of T3 and T4 from Tg. TSH is a 28-kd glycoprotein that is secreted in a pulsatile fashion by the anterior pituitary gland. It has two components. The α subunit is common to other anterior pituitary hormones. However, the β subunit is unique to TSH and determines the hormone's biologic specificity. TSH has specific activity through a receptor on the surface of thethyroid cell. Once the receptor is activated, it interacts with a guanine nucleotide– binding protein (G protein). This interaction stimulates the production of cyclic adenosine monophosphate (AMP). It is through this cyclic AMP pathway that the synthesis of thyroid hormones is mediated. Negative feedback through increased peripheral levels of T3 and T4 can affect TSH secretion. Peripheral T4 is locally deiodinated in the pituitary and converted to T3, which then directly inhibits the release and synthesis of TSH. Excessively large doses of iodide have interesting and complex effects, including an initial increase in organification followed by suppressive effects, a syndrome known as the Wolff-Chaikoff effect.

Disorders of the Thyroid Gland:

Acting through thyroid hormone receptors and , hormones thyroxine (T4) and triiodothyronine (T3) play a critical role in cell differentiation during development and help

maintain thermogenic and metabolic homeostasis in the adult. Autoimmune disorders of the thyroid gland can stimulate overproduction of thyroid hormones (thyrotoxicosis) or cause glandular destruction and hormone deficiency (hypothyroidism).

Laboratory Evaluation[41]

Measurement of Thyroid Hormones

The enhanced sensitivity and specificity of TSH assays have greatly improved laboratory assessment of thyroid function. Because TSH levels change dynamically in response to alterations of T4 and T3, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal, or elevated. With rare exceptions, a normal TSH level excludes a primary abnormality of thyroid function. This strategy depends on the use of immunochemiluminometric assays (ICMAs) for TSH that are sensitive enough to discriminate between the lower limit of the reference range and the suppressed values that occur with thyrotoxicosis. Extremely sensitive (fourth-generation) assays can detect TSH levels 0.004 mU/L, but, for practical purposes, assays sensitive to 0.1 mU/L are sufficient.

The finding of an abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH). Radioimmunoassays are widely available for serum total T4 and total T3.

Total thyroid hormone levels are elevated when TBG is increased due to estrogens (pregnancy, oral contraceptives, hormone therapy, tamoxifen), and decreased when TBG binding is reduced (androgens, nephrotic syndrome). Genetic disorders and acute illness can also cause abnormalities in thyroid hormone binding proteins, and various drugs [phenytoin, carbamazepine, salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs)] can interfere with thyroid hormone binding.

Tests for the end-organ effects of thyroid hormone excess or depletion, such as estimation of basal metabolic rate, tendon reflex relaxation rates, or serum cholesterol, are not useful as clinical determinants of thyroid function.

Hypothyroidism

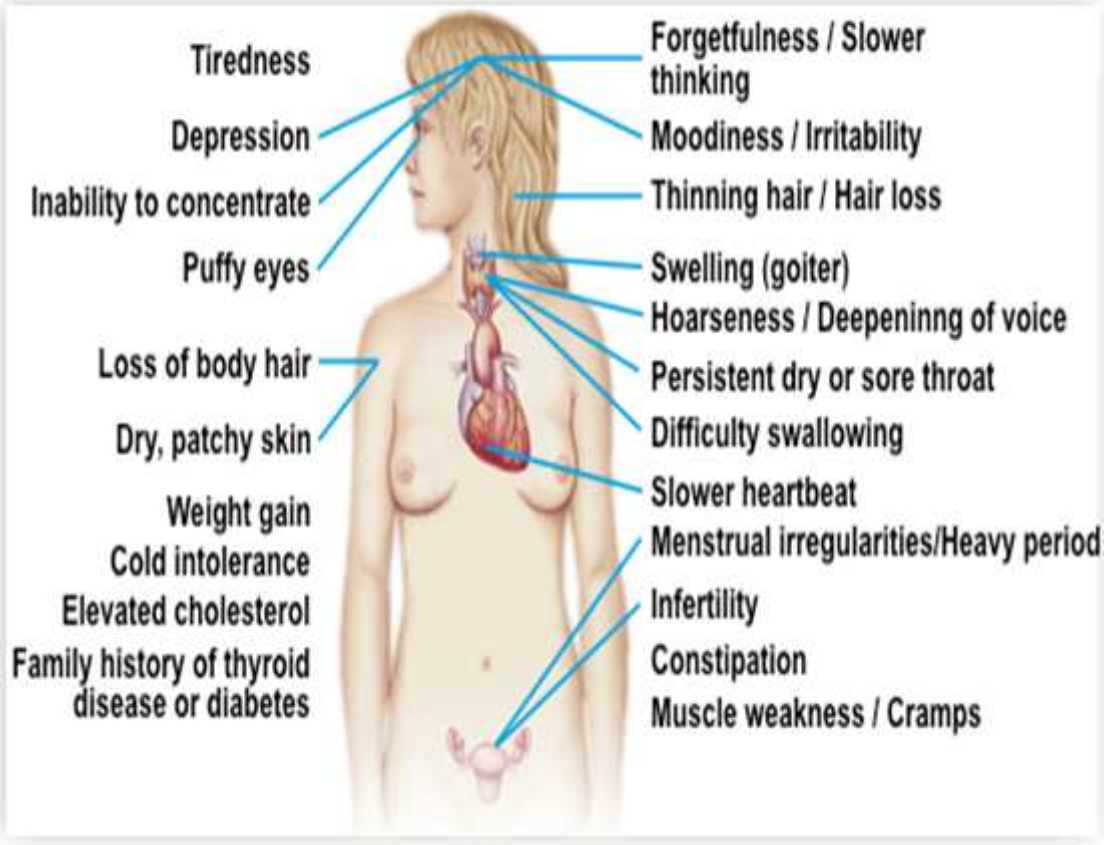
Iodine deficiency remains the most common cause of hypothyroidism worldwide. In areas of iodine sufficiency, autoimmune disease (Hashimoto's thyroiditis) and iatrogenic causes (treatment of hyperthyroidism) are most common.

Causes of Hypothyroidism

Primary
Autoimmune hypothyraidism : Hashimoto’s thyroiditis, atrophic thyroiditis
atrogenic : I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer
Drugs : iodine excess (including iodine-containing contrast media and amiodarone), lithium,

antityroid drugs, ρ-aminosalicylic acid, interferon-α and other cytokines, aminoglutethimide, sunitinib
Congenital hypothyroidism : absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation
Iodine deficiency
Infiltrative disorders : amyloidosis, sarcoidosis, hemochromatosis, sderoderma, cystinosis, Reiedel's thyroiditis
Overexpress of type 3 deoiodinase in infantile hemangioma
Transient
Silent thyroiditis, including postpartum thyroiditis
Subacute thyroiditis
Withdrawal of thyroxine treatment in individual with an intact thyroid
After I treatment or subtotal thyroidectomy for Grave's disease
Secondary
Hypopituitarism : tumours, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies
Isolated TSH deficiency or inactivity
Bexarotene treatment
Hypothalamic disease : tumours, trauma, infiltative disorders, idiopathic

Signs and Symptoms of Hypothyroidism



Autoimmune Hypothyroidism

Autoimmune hypothyroidism may be associated with a goiter (Hashimoto's, or goitrous thyroiditis) or, at the later stages of the disease, minimal residual thyroid tissue (atrophic thyroiditis). Because the autoimmune process gradually reduces thyroid function, there is a phase of compensation when normal thyroid hormone levels are maintained by a rise in TSH. Though some patients may have minor symptoms, this state is called subclinical hypothyroidism. Later, unbound T4 levels fall and TSH levels rise further; symptoms become more readily apparent at this stage (usually TSH >10 mIU/L), which is referred to as clinical hypothyroidism or overt hypothyroidism.

Prevalence

The mean annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women. It is more common in certain populations, such as the Japanese, probably because of genetic factors and chronic exposure to a high-iodine diet. The mean age at diagnosis is 60 years, and the prevalence of overt hypothyroidism increases with age. Subclinical hypothyroidism is found in 6–8% of women (10% over the age of 60). The annual risk of developing clinical hypothyroidism is about 4% when subclinical hypothyroidism is associated with positive TPO antibodies.

Pathogenesis

In Hashimoto's thyroiditis, there is a marked lymphocytic infiltration of the thyroid with germinal center formation, atrophy of the thyroid follicles accompanied by oxyphil metaplasia, absence of colloid, and mild to moderate fibrosis. In atrophic thyroiditis, the fibrosis is much more extensive, lymphocyte infiltration is less pronounced, and thyroid

follicles are almost completely absent. Atrophic thyroiditis likely represents the end stage of Hashimoto's thyroiditis rather than a distinct disorder.

As with most autoimmune disorders, susceptibility to autoimmune hypothyroidism is determined by a combination of genetic and environmental factors, and the risk of either autoimmune hypothyroidism or Graves' disease is increased among siblings. HLA-DR polymorphisms are the best documented genetic risk factors for autoimmune hypothyroidism. Both of these genetic associations are shared by other autoimmune diseases, which may explain the relationship between autoimmune hypothyroidism and other autoimmune diseases, especially type 1 diabetes mellitus, Addison's disease, pernicious anaemia, and vitiligo. The female preponderance of thyroid autoimmunity is most likely due to sex steroid effects on the immune response, but an X chromosome–related genetic factor is also possible and may account for the high frequency of autoimmune hypothyroidism in Turner's syndrome. Environmental susceptibility factors are poorly defined at present.

The thyroid lymphocytic infiltrate in autoimmune hypothyroidism is composed of activated CD4+ and CD8+ T cells as well as B cells. Thyroid cell destruction is primarily mediated by the CD8+ cytotoxic T cells, which destroy their targets by either perforin-induced cell necrosis or granzyme B–induced apoptosis. In addition, local T cell production of cytokines, such as tumor necrosis factor (TNF), IL-1, and interferon , may render thyroid cells more susceptible to apoptosis mediated by death receptors, such as Fas, which are activated by their respective ligands on T cells. These cytokines also impair thyroid cell function directly and induce the

expression of other proinflammatory molecules by the thyroid cells themselves, such as cytokines, HLA class I and class II molecules, adhesion molecules, CD40, and nitric oxide.

Up to 20% of patients with autoimmune hypothyroidism have antibodies against the TSH -R, which, in contrast to TSI, do not stimulate the receptor but prevent the binding of TSH. These TSH-R-blocking antibodies, therefore, cause hypothyroidism and, especially in Asian patients, thyroid atrophy. Their transplacental passage may induce transient neonatal hypothyroidism. Rarely, patients have a mixture of TSI and TSH-R-blocking antibodies, and thyroid function can oscillate between hyperthyroidism and hypothyroidism as one or the other antibody becomes dominant. Predicting the course of disease in such individuals is difficult, and they require close monitoring of thyroid function. Bioassays can be used to document that TSH-

R-blocking antibodies reduce the cyclic AMP–inducing effect of TSH on cultured TSH-R-expressing cells, but these assays are difficult to perform. TBII assays that measure the binding of antibodies to the receptor by competition with radiolabeled TSH do not distinguish between TSI- and TSH-R-blocking antibodies, but a positive result in a patient with spontaneous hypothyroidism is strong evidence for the presence of blocking antibodies. The use of these assays does not generally alter clinical management, although it may be useful to confirm the cause of transient neonatal hypothyroidism.

Clinical Manifestations

The onset is usually insidious, and the patient may become aware of symptoms only when euthyroidism is restored. Patients with Hashimoto's thyroiditis may present because of goiter rather than symptoms of hypothyroidism. The goiter may not be large, but it is usually irregular and firm in consistency. It is often possible to palpate a pyramidal lobe, normally a vestigial remnant of the thyroglossal duct. Rarely is uncomplicated Hashimoto's thyroiditis associated with pain.

Patients with atrophic thyroiditis or late stage of Hashimoto's thyroiditis present with symptoms and signs of hypothyroidism. The skin is dry, and there is decreased sweating, thinning of the epidermis, and hyperkeratosis of the stratum corneum. Increased dermal glycosaminoglycan content traps water, giving rise to skin thickening without pitting (myxedema). Typical features include a puffy face with edematous eyelids and nonpitting pretibial edema. There is pallor, often with a yellow tinge to the skin due to carotene accumulation. Nail growth is retarded, and hair is dry, brittle, difficult to manage, and falls out easily. In addition to diffuse alopecia, there is thinning of the outer third of the eyebrows, although this is not a specific sign of hypothyroidism..

Other common features include constipation and weight gain (despite a poor appetite). In contrast to popular perception, the weight gain is usually modest and due mainly to fluid retention in the myxedematous tissues. Libido is decreased in both sexes, and there may be oligomenorrhoea or amenorrhea in long-standing disease, but menorrhagia is also common.

Fertility is reduced, and the incidence of miscarriage is increased. Prolactin levels are often modestly increased and may contribute to alterations in libido and fertility and cause galactorrhoea.

Myocardial contractility and pulse rate are reduced, leading to a reduced stroke volume and bradycardia. Increased peripheral resistance may be accompanied by hypertension, particularly diastolic. Blood flow is diverted from the skin, producing cool extremities.

Pericardial effusions occur in up to 30% of patients but rarely compromise cardiac function. Though alterations in myosin heavy chain isoform expression have been documented, cardiomyopathy is unusual. Fluid may also accumulate in other serous cavities and in the middle ear, giving rise to conductive deafness. Pulmonary function is generally normal, but dyspnoea may becaused by pleural effusion, impaired respiratory muscle function, diminished ventilatory drive, or sleep apnoea.

Carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps, and pain. On examination, there may be slow relaxation of tendon reflexes and pseudomyotonia. Memory and concentration are impaired. Experimentally, PET scans examining glucose metabolism in hypothyroid subjects show lower regional activity in the amygdala, hippocampus, and perigenual anterior cingulated cortex, among other regions, and this activity corrects after thyroxine replacement. Rare neurologic problems include reversible cerebellar ataxia, dementia, psychosis, and myxedema coma. Hashimoto's encephalopathy has been defined as a steroid-responsive syndrome associated with TPO antibodies, myoclonus, and slow-wave

activity on electroencephalography, but the relationship with thyroid autoimmunity or hypothyroidism is not established. The hoarse voice and occasionally clumsy speech of hypothyroidism reflect fluid accumulation in the vocal cords and tongue.

The features described above are the consequence of thyroid hormone deficiency.

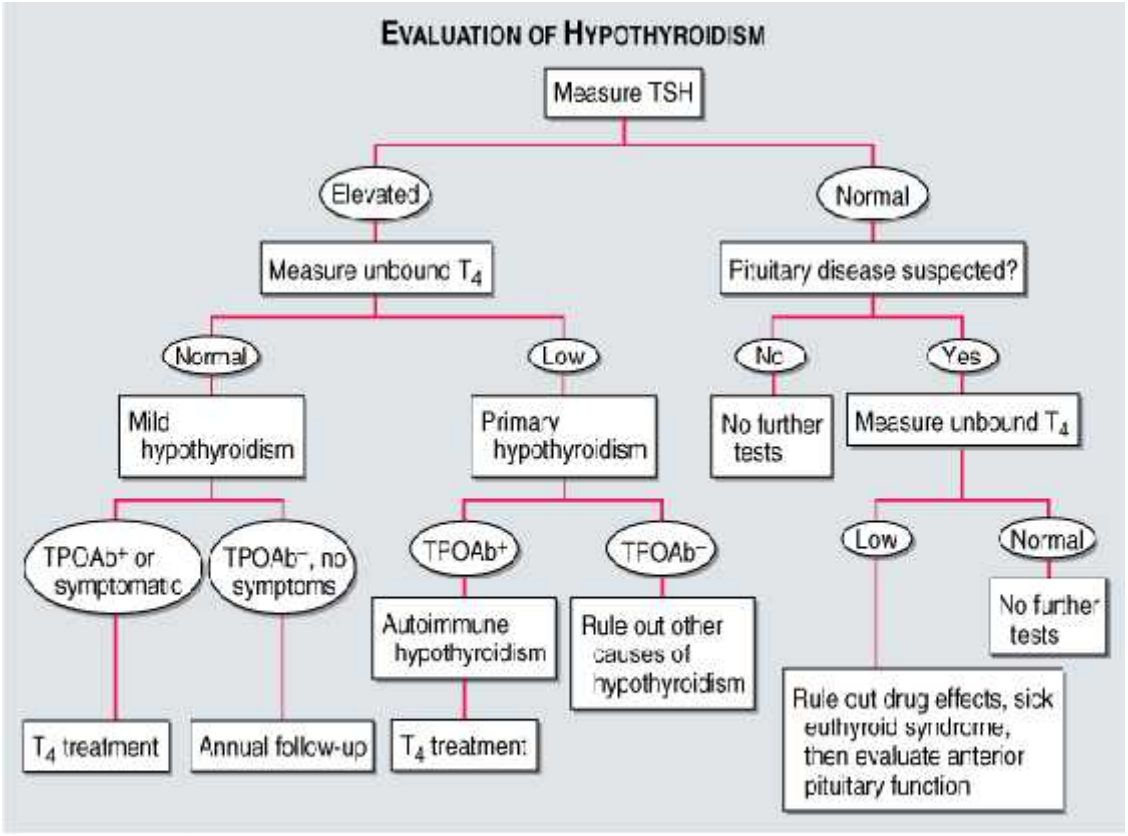


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Fig 6 **: EVALUATION OF HYPOTHYROIDISM**

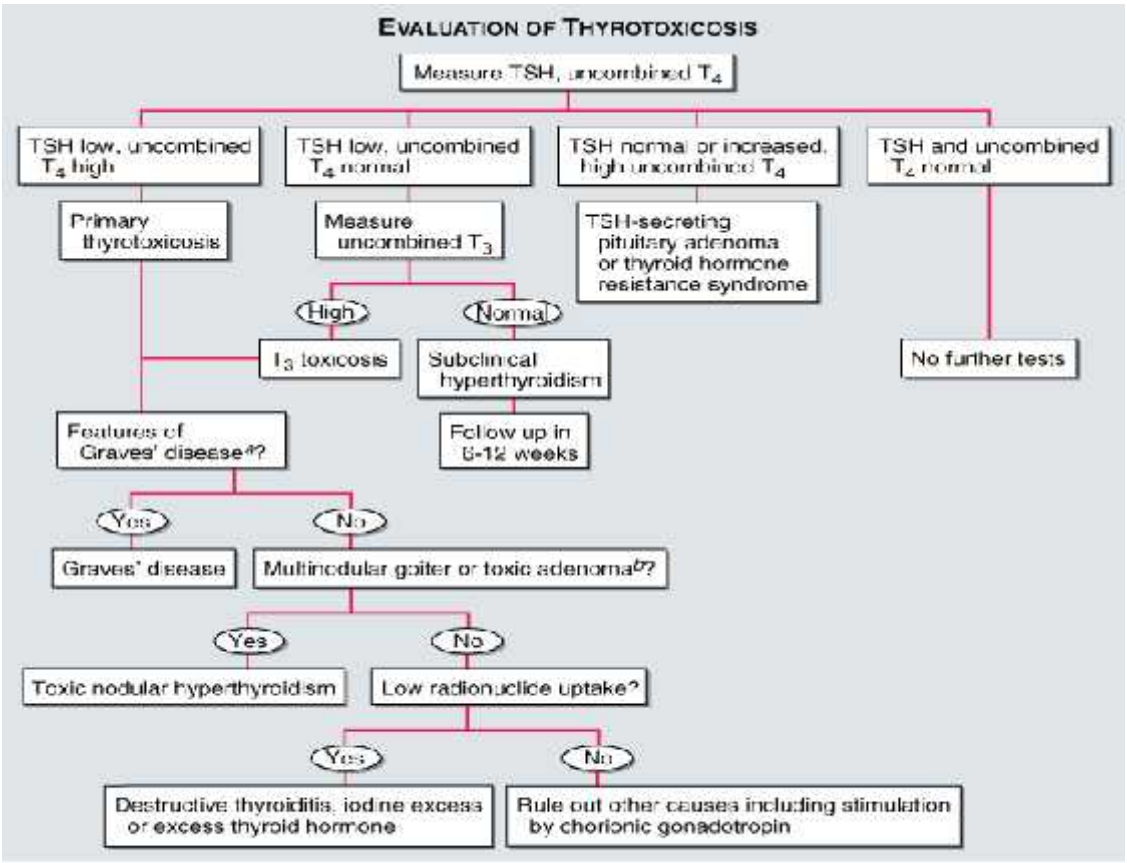

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Fig 7: EVALUATION OF THYROTOXICOSIS

Once clinical or subclinical hypothyroidism is confirmed, the etiology is usually easily established by demonstrating the presence of TPO antibodies, which are present in >90% of patients with autoimmune hypothyroidism. TBII can be found in 10–20% of patients, but these determinations are not needed routinely. If there is any doubt about the cause of a goiter associated with hypothyroidism, FNA biopsy can be used to confirm the presence of autoimmune thyroiditis. Other abnormal laboratory findings in hypothyroidism may include increased creatine phosphokinase, elevated cholesterol and triglycerides, and anemia (usually

normocytic or macrocytic). Except when accompanied by iron deficiency, the anemia and other abnormalities gradually resolve with thyroxine replacement.

TREATMENT:

Clinical Hypothyroidism

If there is no residual thyroid function, the daily replacement dose of levothyroxine is usually 1.6 g/kg body weight (typically 100–150 g). In many patients, however, lower doses suffice until residual thyroid tissue is destroyed. Adult patients under 60 without evidence of heart disease may be started on 50–100 g levothyroxine (T4) daily. The dose is adjusted on the basis of TSH levels, with the goal of treatment being a normal TSH, ideally in the lower half of the reference range. TSH responses are gradual and should be measured about two months after instituting treatment or after any subsequent change in levothyroxine dosage. The clinical effects of levothyroxine replacement are slow to appear. Patients may not experience full relief from symptoms until 3–6 months after normal TSH levels are restored. Adjustment of levothyroxine dosage is made in 12.5- or 25-g increments if the TSH is high; decrements of the same magnitude should be made if the TSH is suppressed. Patients with a suppressed TSH of any cause, including T4 overtreatment, have an increased risk of atrial fibrillation and reduced bone density.

Although dessicated animal thyroid preparations (thyroid extract USP) are available, they are not recommended because the ratio of T3 to T4 is nonphysiologic. The use of levothyroxine combined with liothyronine (triiodothyronine, T3) has been investigated, but benefit has not been confirmed in 30 prospective studies. There is no place for

liothyronine alone as long-term replacement, because the short half-life necessitates three or four daily doses and is associated with fluctuating T3 levels.

Once full replacement is achieved and TSH levels are stable, follow-up measurement of TSH is recommended at annual intervals and may be extended to every 2–3 years if a normal TSH is maintained over several years. It is important to ensure ongoing adherence, however, as patients do not feel any symptomatic difference after missing a few doses of levothyroxine, and this sometimes leads to self-discontinuation.

In patients of normal body weight who are taking 200 g of levothyroxine per day, an elevated TSH level is often a sign of poor adherence to treatment. This is also the likely explanation for fluctuating TSH levels, despite a constant levothyroxine dosage. Such patients often have normal or high unbound T4 levels, despite an elevated TSH, because they remember to take medication for a few days before testing; this is sufficient to normalize T4, but not TSH levels. It is important to consider variable adherence, because this pattern of thyroid function tests is otherwise suggestive of disorders associated with inappropriate TSH secretion . Because T4 has a long half-life (7 days), patients who miss a dose can be advised to take two doses of the skipped tablets at once. Other causes of increased levothyroxine requirements must be excluded, particularly malabsorption (e.g., celiac disease, small-bowel surgery), estrogen therapy, and drugs that interfere with T4 absorption or clearance such as cholestyramine, ferrous sulfate, calcium supplements, lovastatin, aluminum hydroxide, rifampicin, amiodarone, carbamazepine, and phenytoin.

Subclinical Hypothyroidism

By definition, subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of hypothyroidism. There are no universally accepted recommendations for the management of subclinical hypothyroidism, but the most recently published guidelines do not recommend routine treatment when TSH levels are below 10 mU/L. It is important to confirm that any elevation of TSH is sustained over a 3- month period before treatment is given. As long as excessive treatment is avoided, there is no risk in correcting a slightly increased TSH. Moreover, there is a risk that patients will progress to overt hypothyroidism, particularly when the TSH level is elevated and TPO antibodies are present. Treatment is administered by starting with a low dose of levothyroxine (25–50 g/d) with the goal of normalizing TSH.

Physical Examination

Examination of the neck begins by inspecting the seated patient from the front and side and noting any surgical scars, obvious masses, or distended veins. The thyroid can be palpated with both hands from behind or while facing the patient, using the thumbs to palpate each lobe. It is best to use a combination of these methods, especially when nodules are small. The patient'sneck should be slightly flexed to relax the neck muscles. After locating the cricoid cartilage, the isthmus can be identified and followed laterally to locate either lobe (normally, the right lobe is slightly larger than the left). By asking the patient to swallow sips of water, thyroid consistency can be better appreciated as the gland moves beneath the examiner's fingers.

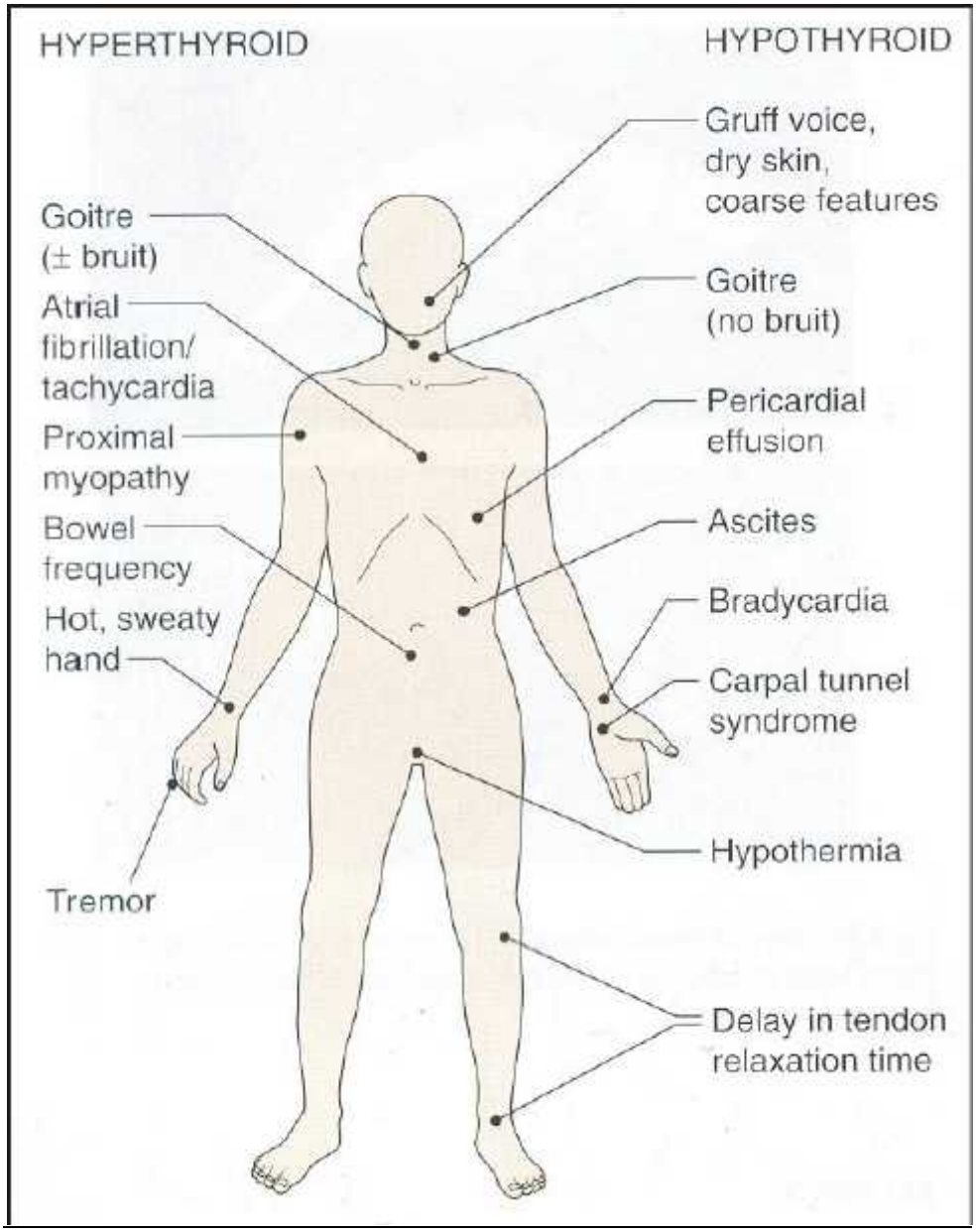
Features to be noted include thyroid size, consistency, nodularity, and any tenderness or fixation. An estimate of thyroid size (normally 12–20 g) should be made, and a drawing is often the best way to record findings. The size, location, and consistency of any nodules should also be defined. A bruit over the gland indicates increased vascularity, as occurs in hyperthyroidism. If the lower borders of the thyroid lobes are not clearly felt, a goiter may be retrosternal. Large retrosternal goiters can cause venous distension over the neck and difficulty breathing, especially when the arms are raised (Pemberton's sign). With any central mass above the thyroid, the tongue should be extended, as thyroglossal cysts then move upward. The thyroid examination is not complete without assessment for lymphadenopathy in the supraclavicular and cervical regions of the neck.

PATTERNS OF THYROID FUNCTION TEST RESULTS IN PATIENTS WITH THYROID DISEASE[42]

Type of disease	T4	T3	TSH
Conventional hyperthyroidism (95% of cases)	Raised	Raised	Undetectable
T3 hyperthyroidism (5% of cases)	Normal[1]	Raised	Undetectable
Subclinical hyperthyroidism	Normal[1]	Normal[1]	Undetectable
Primary hypothyroidism	Low	Not indicated[2]	Raised (usually >20m U/L)
Subclinical hypothyroidism	Normal[3]	Not indicated[2]	Raised
Secondary hypothyroidism i.e. pituitary or hypothalamic disease	Low	Not indicated[2]	Usually undetectable[4]
Non thyroidal illness	Raised	Low, normal or raised[5]	Usually undetectable.

1. Usually upper part of reference range
2. Measurement of T3 is not a sensitive indicator of hypothyroidism and should not berequested.
3. Usually lower part of reference range
4. May be normal or even slightly raised due to the production of immunreactive forms of TSH which have no biological activity.
5. Depending on the assay system.

Fig 8:Features of hyper and hypothyroidism



DYSFUNCTIONAL UTERINE BLEEDING (DUB) AND ITS CLASSIFICATION

Dysfunctional uterine bleeding is defined by various authors in many waysleading to confusion as to, which are the exact entities, which come under thisheading.

NOVAK defines it as “bleeding without a causative uterine lesion such as tumor infection or complications of pregnancy, although frequently there may be associated cysts of the ovary”.

SUTHERLAND defines DUB as “Abnormal uterine bleeding which is not explained by any palpable lesions of the reproductive organs”.[43]

CROSSEN defines it as “irregular, excessive, scanty or prolonged bleeding of endometrial origin, occuring without neoplasia, infection, pregnancy, blood dyscrasias, trauma or hormone

administration”.[44]

TAYLOR restricts the term DUB to be applied only when all possible causes for irregular, excessive or prolonged bleeding have been excluded. Such as exclusive approach would tend to eliminate from consideration any uterine bleeding for which an etiology has been uncovered.[45]

TELINDE defines DUB as a symptom complex that in absence of pregnancy, neoplasm,

infection or intrauterine lesions.[46]

SPEROFF describes DUB variety of bleeding manifestations of anovulatory cycles (in absence of pathology or medical illness).[47]

JEFFCOATES defines it as “excessive, prolonged, unpatterned bleeding from the endometrium unrelated to structural or systemic disease and thus other diagnosis must be excluded.[48]

DEWHURST defines DUB as “abnormal bleeding from the uterus in the absence of organic disease of the genital tract”.[49]

DAWN refers it as a excessive uterine bleeding where no organic, systemic, haematologic or pelvic cause can be detected.[50]

Two areas of general agreement can be obtained from these sources – first, the necessity to exclude bleeding arising from organic disorders of the reproductive tract in order that an entity may qualify as DUB.

Secondly, the presupposition that endocrinologic abnormalities have a significant relationship to DUB. Adequate clinical examinations of abdomen and pelvis, uterine curettage, hysteroscopy or atleast an endometrial biopsy are essential to exclude organic disease of the uterus. In recurrent severe abnormal uterine bleeding repeat curettage should be done to avoid previously missed organic disease.[1]

Hence, a provisional diagnosis of DUB is made clinically.

Classification of DUB

Ovular haemorrhages

1. Functional epimenorrhagia and epimenorrhoea

2. Functional menorrhagia

• Irregular ripening of the endometrium

• Prolonged or irregular ripening of the endometrium

Anovular haemorrhage

1. Threshold bleeding

2. Metropathia haemorrhagica

BAIRD (1985) tried to classify possible endocrine abnormalities and endometrial histologic patterns and possible associated clinical presentation.[47]

Type	Endocrine abnormality and endometrial histology	Typical bleeding pattern
Normal (ovulatory)	normal endometrium Normal (ovulatory)	Polymenorrhoea Menorrhagia.
	Long cycle → long proliferative phase, normal endometrium	Oligomenorrhoea Menorrhagia.
Corpus luteum abnormality	Insufficiency → Short luteal phase, irregular or deficient secretory endometrium	Premenstrual spotting Menorrhagia
	Persistent (Halban's disease) - Irregular endometrial shedding	Prolonged menstruation
Anovulatory	Insufficient fo llicles → Short cycles, inadequate proliferative or atrophic endometrium	Polymenorrhoea Metrorrhagia
	Persistent follicles or PCO → prolonged cycle, proliferative or hyperplastic endometrium	Oligomenorrhoea Metropathia aemorrhagica.

Definition of menstrual cycle abnormalities (NOVAK)[28]

- Oligomenorrhoea : Infrequent irregular episodes of bleeding, usually occurring at interval of more than 35 days. Polymenorrhoea : Frequent but regular episodes of uterine bleeding usually occuring at intervals of 21 days or less.
- Menorrhagia: Uterine bleeding usually excessive and prolonged occurring atregular intervals.
- Menometrorhagia : Uterine bleeding usually excessive and prolonged occurring at frequent irregular intervals. Hypomenorrhoea : Uterine bleeding that is regular but decreased in amount.
- Intermenstrual bleeding : Uterine bleeding usually not excessive occurring between regular menstrual periods.
- Metrorrhagia – Irregularly timed bleeding

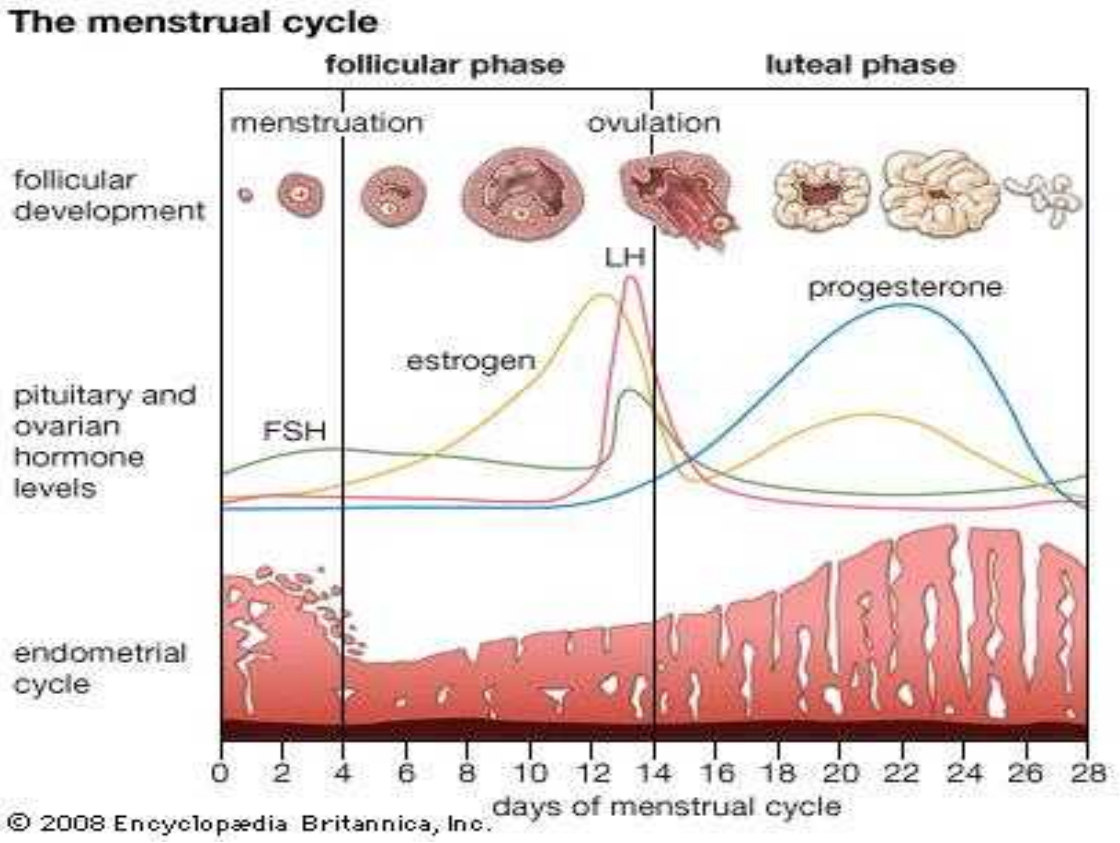


Fig 9:Relationship Between Endocrine, Ovarian And Endometrial Cycles

PHYSIOLOGY OF MENSTRUATION

Menstruation is the cyclical uterine bleeding occurring during reproductive age between menarche and menopause. Normal menstruation represents the cyclical shedding of secretory endometrium and is essentially a progesterone withdrawal bleeding caused by degeneration of corpus luteum if the ovum is not fertilized.[49]

The endometrium is composed of glands and stroma, and has the following layers, a superficial functional layer 'decidua functionalis' (which is further divided into stratum compartum & stratum spongiosum) responding to hormones. The basal layer 'decidua basalis' is responsible for the regeneration of the endometrium.

Under the influence of monthly cyclic production of estrogen and progesterone by ovaries, endometrium undergoes cyclic changes through the following phases2:

- Proliferative phase

- Secretory phase

- Menstrual phase

Proliferative phase

It Corresponds to the follicular phase of the ovarian cycle. It follows the menstrual phase and concludes at ovulation. During this phase estrogen from the growing follicle causes regeneration of the endometrium from the basalis layer.

VEGF is a highly potent endothelial nitrogen produced by the endometrium in response to the rising estrogen and associated hypoxia.3 Short, narrow and straight glands become longer and tortuous due to estrogen influence and stroma becomes dense and compact.

Secretory phase

This is the progestrational phase of endometrial cycle which begins after ovulation. It corresponds to the luteal phase of the ovarian cycle, it extends from ovulation till onset of next menses.

The progesterone dominated secretory phase bring about secretory changes in the estrogen

primed endometrium with the primary aim to produce appropriate environment for implantation.

The histopathological examination of the endometrium during secretory phase gives typical ‘saw toothed’ and ‘cork screw’ appearance in the cross section.[29] At the peak of secretory phase one week after ovulation the endometrial thickness is about 5 to 6 mm. If the ovum is not fertilized, the corpus luteum degenerates and menstruation starts around 14th day after ovulation.

Menstrual phase

Shedding of endometrium takes place during this phase and it lasts for about 3 to 5 days.

Regulation of menstrual cycle (endocrine control)

The hypothalamo-pitutary axis The hypothalamus secretes the gonadotrophin releasing hormone (GnRH), with varying frequency and amplitude leading to the release of follicle stimulating hormone(FSH) and luteinising hormone(LH) from the anterior pituitary gland.

- The follicular phase shows high amplitude more frequent pulses withfrequency increasing before LH surge with dominance of FSH
- The luteal phase has low amplitude, less frequent pulses leading to thepredominance of LH
- One pulse every hour is typical of follicular phase and one pulse every 2 to 3 hours is typical of luteal phase[51]

Criteria for normal menstrual cycle

Menstrual cycle is judged by three clinical parameters

Cycle length:

It is the interval between the first day of one period and the first day of the next.[51]

During the active reproductive years, menstruation occurs at approximately 28 +/- 7 days. Each woman has her own rhythm which may change after marriage or child birth.[49]

Treloar et al reported at university of Minnesota in his prospective study over 30 years in Caucasian women that the cycle length usually varies by 1 to 2 days each month and only 50 % women have cycles within 26-30 days range.

Median cycle length declines from 28.87 (+/-2.75) days at age of 20 years to median of 26.8(+/-2) days by 40 years of age.[52]

In reference to this study, in general cycles with length less than 24 days are considered polymenorrhoea and those with more than 35 days are considered oligomenorrhoea.

Regularity of cycle length depends upon HPO axis. The immediate post menarche cycles are irregular and long due to immaturity of hypothalamus and pituitary, as a result of which regular

ovulation is yet to be established. Again in perimenopausal period cycles become irregular and mostly longer due to diminished number of follicles with increased resistance to gonadotrophin stimulation.1

Duration of menstrual blood loss:

As per Gullibaud and Bonner (1978), normal range of duration of bleeding is 2 to 7 days with an average of 5 days. Shorter (hypomenorrhea) or longer (hypermenorrhea) than this is considered abnormal.[53]

Menstrual blood loss:

Average blood loss per cycle is considered to be 35-40 cc. This is equivalent to daily loss of 0.6 mg to 0.7 mg of iron throughout each month.[49]

According to Rybo et al (1985) parity has a small effect on MBL, multiparas have a slightly higher average loss than nulliparas.[54]

WHO report mentions that in western European populations, the average blood loss during menstruation varies from 31-39 ml while Chinese and Japanese populations it is 47-54 ml and 52-56 ml respectively.[55]

In Swedish population, Hallberg et al observed significant increase in the incidence of iron deficiency anaemia when the MBL was 80 ml or more.[56]

Following are the terminologies used for describing abnormal bleeding pattern.[51]

Menorrhagia: is prolonged (> 7 days) and /or excessive (>80ml) uterine bleeding that occurs at regular intervals.

Polymenorrhoea: is uterine bleeding that occurs at regular intervals less than 21 days apart.

Oligomenorrhoea: is infrequent uterine bleeding that occurs at intervals more than 35 days apart. Metrorrhagia: is uterine bleeding that occurs at irregular but frequent intervals, the amount of uterine bleeding is variable and the duration of flow is often prolonged.

Menometrorrhagia: prolonged uterine bleeding that occurs at irregular intervals.

PATHOPHYSIOLOGY OF DUB

There are three reasons for the self-limited character of estrogenprogesterone withdrawal bleeding.

- It is a universal endometrial event: menstrual changes occur simultaneously in all segments of the endometrium.
- The estrogen primed endometrial tissue which has responded to appropriate levels of progesterone is structurally stable, and random breakdown of tissue due to fragility is avoided.
- Inherent in the events that preclude the onset of menstruation are factors involved in stopping menstrual flow.

Platelets and fibrin play a direct role in the homeostasis achieved in a bleeding menstrual

endometrium. Intravascular thrombi are seen in the functionalis layer and are localised to the shedding surface of the tissue. Fibrinolysis occurs in the endometrial tissue limiting fibrin deposition in the proximal, still unshed layer.

After early dependence on thrombin plugs to restrain blood loss, later generalised vasoconstrictive homeostasis without thrombin plugs occur.

In the past decade, studies have shown increased endometrial fibrinolysis and an alteration in prostaglandin balance as local uterine abnormalities present in dysfunctional uterine bleeding.

- Increase PGE2 and F2alpha.
- Increase endometrial fibrinolysis
- Structural changes in the spiral arterioles and venous sinuses of endometrium such as perivascular fibrosis, subendothelial hyaline degeneration, hyperplasia and hypertrophy of smooth muscle and elastosis(salvator, 1958)
- Abnormal vascularity of the endometrium.
- Delayed regeneration of the endometrium
- Excessive endometrial tissue necrosis by hydrolytic enzymes from Golgilysosomal complex.
- Deficient formation and release of endometrial vasoconstrictor substance.

ANOVULATORY BLEEDING[38,39]

Anovulation or oligo-ovulation is the commonest cause of abnormal uterine bleedingwhen no organic cause has been found. The characteristic feature is the absence of active corpus luteum tissue in the ovary. A follicle ripens but fails to rupture, the ovum dies and follicle may go onto cyst formation whether it forms a cyst or not, it produces oestrogen for time and this act on the uterus without being opposed by progesterone.

The production may be continuous at a moderate level, or intermittently high and low. In either case the uterus responds by hypertrophy of its myometrium and endometrium, and the latter may become polypoidal. On section the endometrium shows the picture of hyperplasia, usually of cystic type (SWISS CHEESE) but occasionally adenomatous.

Bleeding is acyclical it is continuous for 2-8 weeks and can be so heavy as to threaten life. In about half the cases it is preceded by a short period of amenorrhoea which coincides with a continuously high production of oestrogen by the follicle and this type of clinical picture was earlier often labelled as metropathia haemorrhagica. When the granulosa cells becomes less active or when the endometrium grows so thick that the supply of oestrogen becomes relatively inadequate, oestrogen withdrawal bleeding takes place. The bleeding is always painless. On examination the uterus feels slightly enlarged and its sometimes possible to palpate cystic ovaries. A definitive diagnosis is only by histological examination of curettings.

The underlying cause is unknown personally the failure in ovulation, reflects an abnormal gonadotrophin stimulus. Behind this there is often a hypothalamic and cortical basis, as in the case of other forms of dysfunctional bleeding, being mostly seen in nervously tense and emotional subjects. It recurs most commonly during the few years preceding the menopause, but is occasionally seen in girls aged 12-20 years. In the latter it shows a strong tendency to spontaneous cure.

INVESTIGATIONS

There is no one clear sequence to use of endometrial biopsy, TVS, SIS, and hysteroscopy when evaluating abnormal uterine bleeding. None of these will distinguish all anatomic lesions with high sensitivity and specificity. That said, USG for several reasons is a logical first step. It is well-tolerated, cost-effective, and requires relatively minimal technical skill. Additionally, it has the advantage of reliably determining whether a lesion is diffuse or focal. Once anatomic lesions have been identified, subsequent evaluation requires individualization. If endometrial hyperplasia or cancer is suspected, then endometrial biopsy may offer advantages. Alternatively possible focal lesions may be best investigated with either hysteroscopy or SIS. Ultimately, the selection of appropriate tests depends on their accuracy to characterize the most likely anatomic lesions.

MATERIAL AND METHODS

Source of data

This study will be carried out in the department of Obstetrics and Gynaecology, at BLDE University's Shri. B. M. Patil Medical College, Hospital and Research Center, Bijapur from October 2012 to June 2014. 140 women with a provisional diagnosis of dysfunctional uterine bleeding from our hospital will be selected for the study.

Study Design **:** A prospective study

Study Period **:** 18 Months (December 2012 to August 2014)

DETAILS OF THE STUDY

INCLUSION CRITERIA

- All cases provisionally diagnosed to have dysfunctional uterine bleeding from puberty to premenopausal age groups.

- All patient having major complaint of menstrual disturbances e.g., menorrhagia, polymenorrhoea, polymenorrhagia, metropathia hemorrhagica, metrorrhagia, Oligo and hypomenorrhoea.

EXCLUSION CRITERIA

- Patients who are on Antithyroid drug or thyroid hormones, IUCD users, history of bleeding disorder will be excluded.
- Patients with organic lesions of genital tract.

Procedure of Study

• A detailed history was obtained with special relevance to age, bleeding pattern.

• Onset, duration, amount of bleeding, complaints related to thyroid dysfunction was noted in detail.

• A thorough clinical examination including general physical examination, neck examination, gynaecological, and systemic examination was carried out, with special reference to thyroid dysfunction; in cases with a provisional clinical diagnosis of DUB.

• Patients having thyroid disease were excluded.

• All these patients were subjected to routine investigations like hemoglobin percentage, blood counts, urine examination for albumin, sugar, microscopy, bleeding time, clotting time, (to rule out coagulation defect) and USG Abdomen & peivis.

• Then all patients were subjected for T3, T4, TSH and TPOAb estimation in their sera.

Investigations were estimated by Chemiluminescence Immuno Assay (C.L.I.A) method using reagent Monobind I N C; USA;Kit. with the help of fully automatic Alpha lite machine in Bio-chemical lab at Bijapur.

Drop of reagent monobind I N C mixed with collected blood and using special programming chart they place it in the fully automatic analyzing machine Alphalite, made in FRANCE.

These test will be done in fasting blood samples.

The following are noted.

- Level of T3.
- Level of T4.
- Level of TSH.
- Level of TPO antibody.

Patients will then be grouped into 4 categories

- Euthyroid
- Subclinical hypothyroid
- Hypothyroid
- Hyperthyroid

Patients found to have thyroid dysfunction will be referred to physician for further management.

SAMPLE SIZE

With incidence rate of DUB 10 percent, at 95 percent confidence interval and at ± 5 margin of error the worked out sample size is 138.

$$N = z\alpha^2 \ X \ p \ X \ q \ / \ d^2$$

Hence 140 cases will be included in the study.

STATISTICAL ANALYSIS:

Data will be presented by-

1.Mean ± SD

2.Diagrams &

Will be analysed by statistical test One-way ANOVA.

OBSERVATION AND RESULTS

The following are the tables from the data of the study to provide a descriptive analysis of various factors and their association with each other.

According to the table the maximum number of patients in the study belong to the age group 31-40 years, 57 cases which accounted to 41%, 45 cases belong to the age group of above 40 years, 22 cases are below the age of 20 years. The age group 21-30 years has 16 cases which accounted for 11%.

Table 1: Distribution of Patients According to Age

Age	Number of cases	Percent
<20	22	15.7
21-30	16	11.4
31-40	57	40.7
>40	45	32.1
Total	140	100

Graph 1: Distribution of Patients According to Age

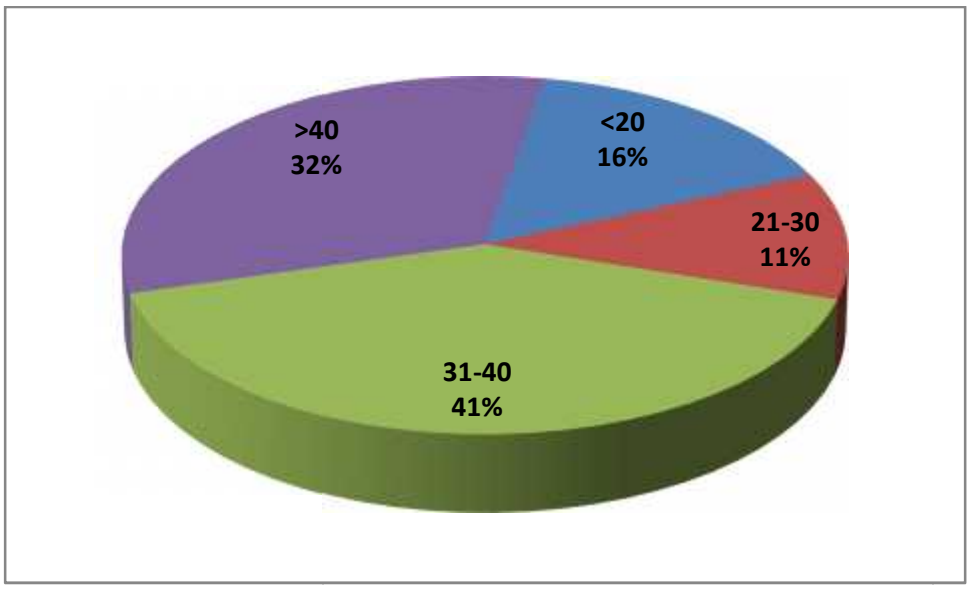


Table 2: Distribution of Patients According to Symptoms

Type of Bleeding	Number of cases	Percent
Acyclical	20	14.6
Menorrhagia	62	44.3
Metrorrhagia	5	3.6
Oligomenorrhoea	13	9.3
Polymenorrhoea	13	9.3
Polymenorrhagia	27	19.3
Total	140	100

The above column shows 140 patients who came with the complaint of different bleeding pattern. Commonest was menorrhagia 44%. Among others 19% of cases presented with polymenorrhagia,15 % with Acyclical, 9% with Oligomenorrhoea and polymenorrhoea and 4% had metrorrhagia. Maximum patients were seen with complaint of menorrhagia.

Graph 2: Distribution of Patients According to Symptoms

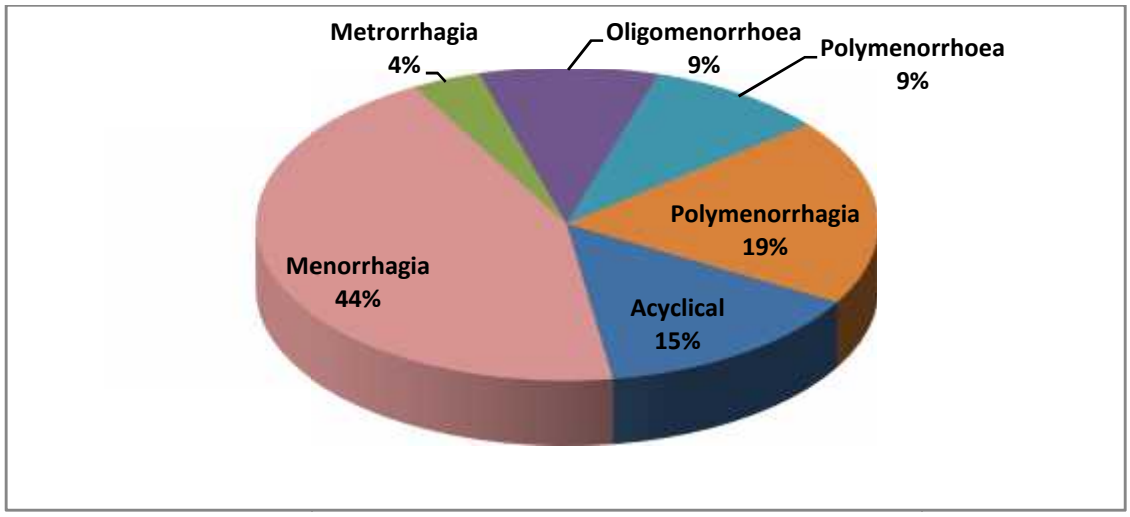


Table 3: Distribution of Patients According to Parity

Parity	Number of cases	Percent
Unmarried	25	17.9
0	17	12.1
1	19	13.6
2	46	32.9
3	24	17.1
4 or more	9	6.4
Total	140	100

The above column shows relationship of DUB with parity. Among 140 cases of DUB 25 patients were unmarried 18% and nulliparas were 17(12%). 19(14%) patients wer para 1, 46(33%) patients were para 2, 24(17%) patients were para 3 and 9(6%) patients with 4 or more parity. In this study maximum number of patients were of para 2 and minimum number of patient presenting as clinical DUB cases were of para 4 or more.

Graph 3: Distribution of Patients According to Parity

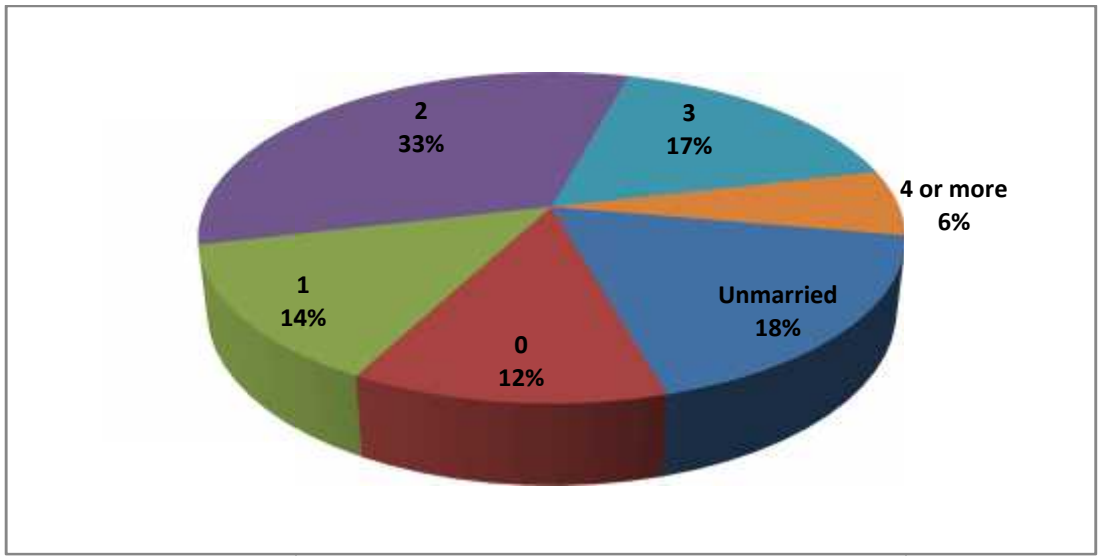


Table 4: Distribution of Patients According to Thyroid Function

Thyroid Function	Number of cases	Percent
Euthyroid	123	87.9
Hypothyroid	5	3.6
Subclinical thyroid	10	7.1
Hyperthyroid	2	1.4
Total	140	100

This column shows the prevalence of various thyroid dysfunctions among the 140 cases included in the study. The prevalence of sub clinical hypothyroidism is 7%, there were 5 hypothyroid cases among the 140 cases (4%), there was 2 hyperthyroid case among the 140 cases (1%). The total thyroid disorders associated for 12%. The most common thyroid dysfunction among the study group was sub clinical hypothyroidism (7%).

Graph 4: Distribution of Patients According to Thyroid Function

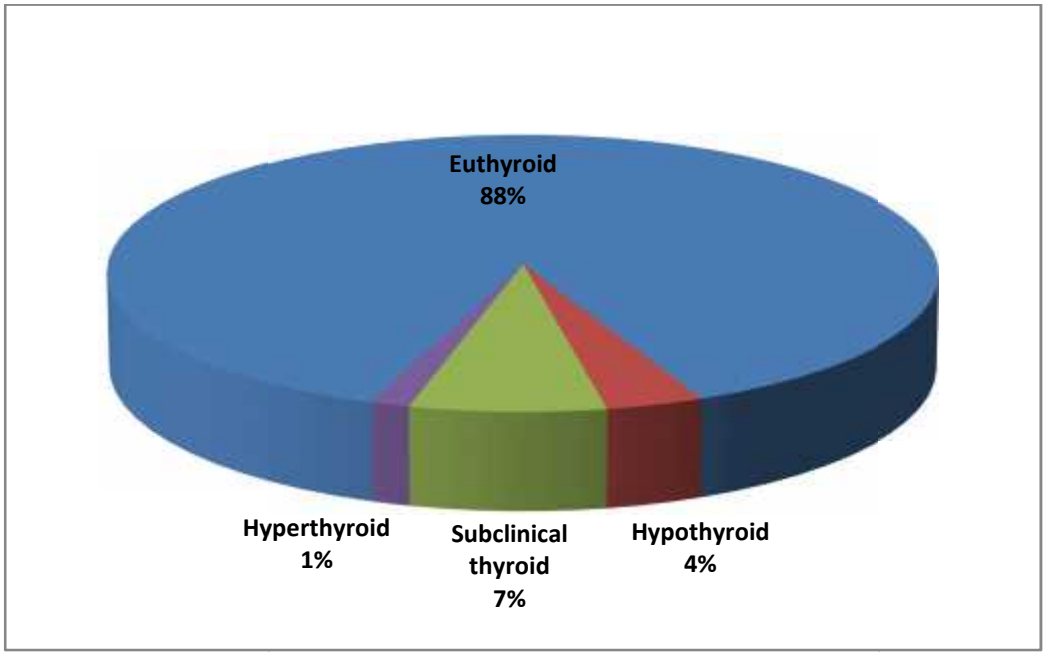
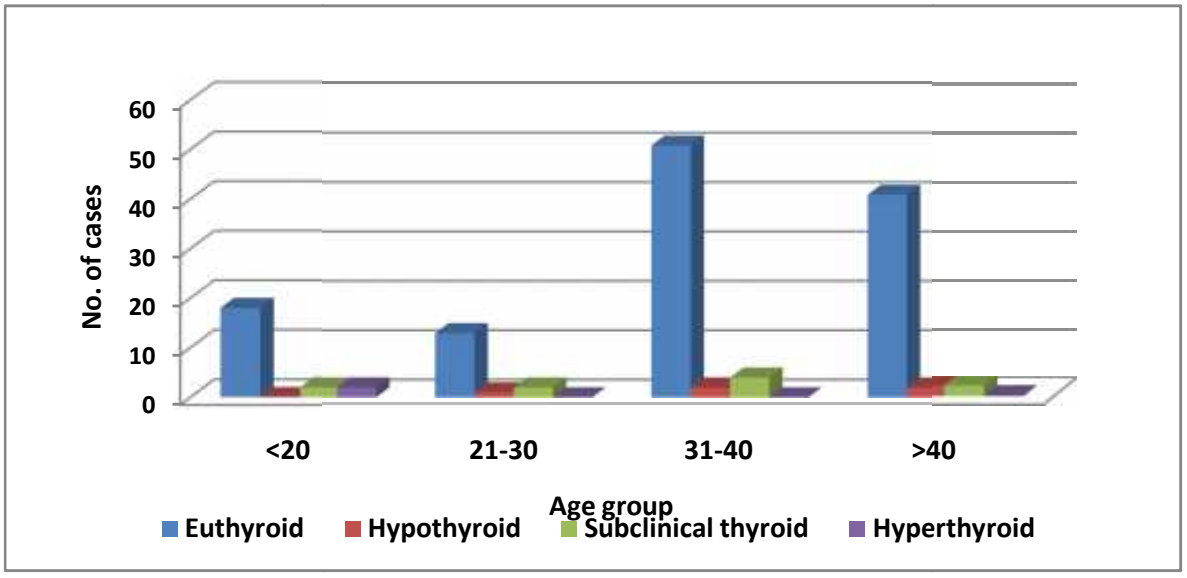


Table 5: Distribution of Patients According to age and thyroid disorder

Age	Euthyroid	Hypothyroid	Subclinical hypothyroid	Hyperthyroid	Total
<20	18	0	2	2	22
21-30	13	1	2	0	16
31-40	51	2	4	0	57
>40	41	2	2	0	45
Total	123	5	10	2	140

This table shows the incidence of thyroid dysfunction in different age groups. Below the age of 20 years, 18 cases were euythroid, 2 had sub clinical hypothyroidism and 2 had hyperthyroidism. Among the cases belonging to 21-30 years, 13 cases were euthyroid and 1 had hypothyroidism and 2 had subclinical hypothyroidism. Among the age group of 31-40 years, 51 patients were euthyroid, 2 had hypothyroidism and 4 had subclinical hypothyroidism. Above the age of 40 years,2 patients had hypothyroidism, 2 patients had sub clinical hypothyroidism.

Graph 5: Distribution of Patients According to age and thyroid disorder

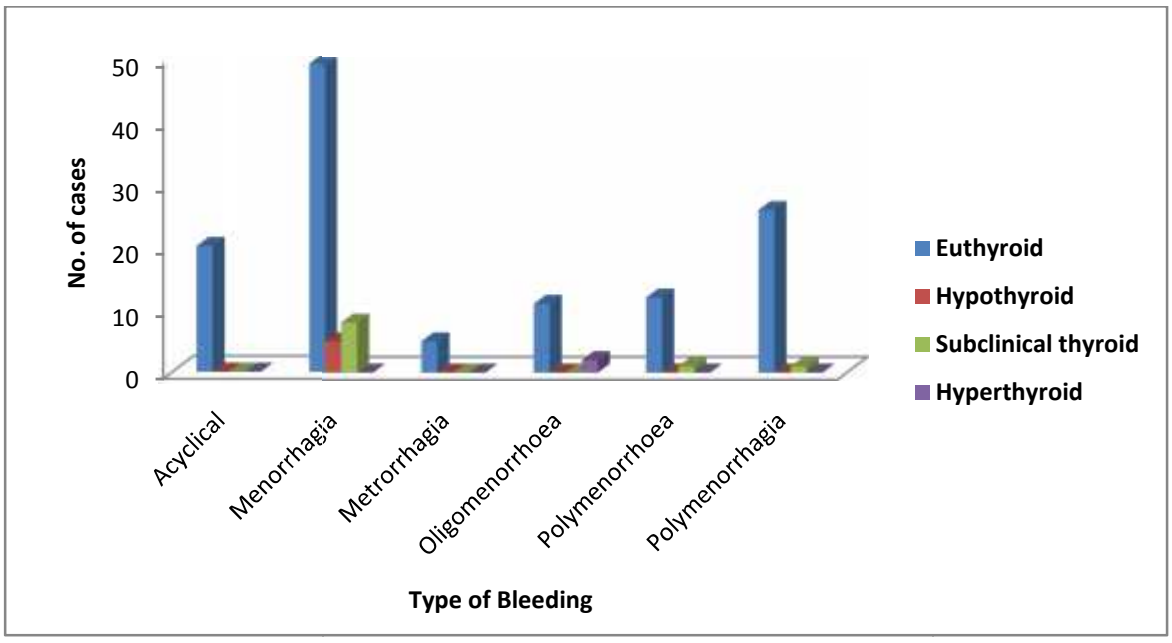


The following table describes the various distribution of patients according to their thyroid dysfunction in relation to their abnormal bleeding pattern. Patients who presented with menorrhagia have prevalence of 26% of thyroid dysfunction, this appears to be the most common bleeding pattern according to this study to be associated with thyroid disorders. Patients who presented with oligomenorrhoea had 18% prevalence of thyroid disorder.

Table 6: Bleeding Pattern in Thyroid Dysfunction

Type of Bleeding	Thyroid Dysfunction				Total
	Euthyroid	Hypothyroid	Subclinical Hypothyroid	Hyperthyroid	
Acyclical	20	0	0	0	20
Menorrhagia	49	5	8	0	62
Metrorrhagia	5	0	0	0	5
Oligomenorrhoea	11	0	0	2	13
Polymenorrhoea	12	0	1	0	13
Polymenorrhagia	26	0	1	0	27
Total	123	5	10	2	140

Graph 6: Bleeding Pattern in Thyroid Dysfunction

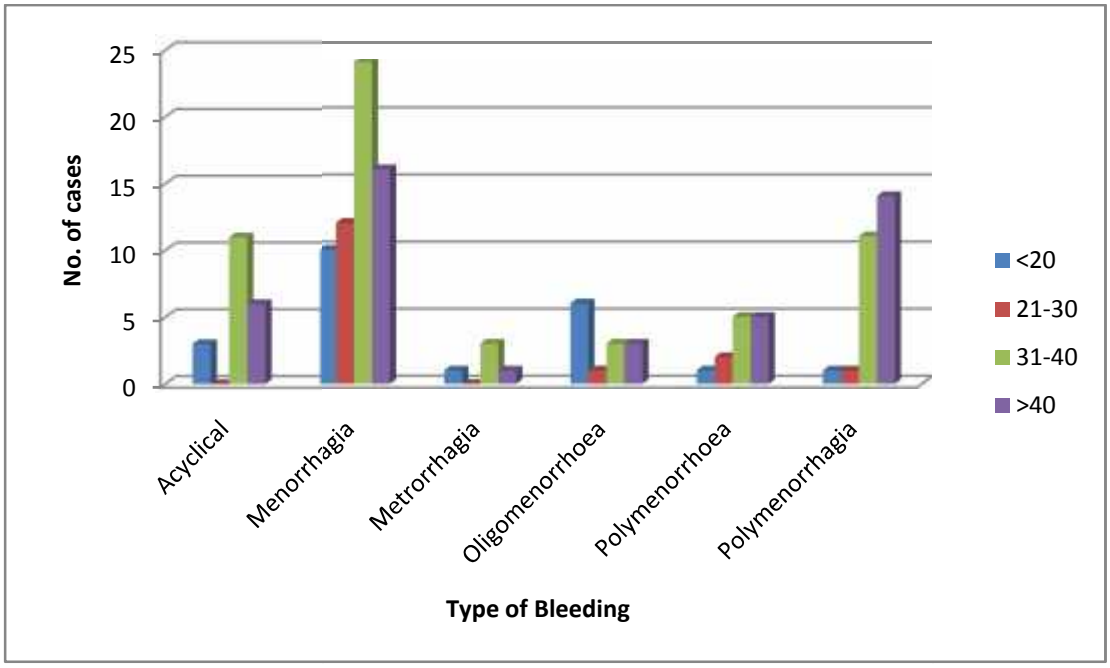


This table shows the distribution according to age group and bleeding pattern menorrhagia is the most common bleeding pattern 45%(10 cases) in age group less than 20 years, 75%(12 cases) in age group 21 – 30 years, 42%(24 c0ases) in age group 31 – 40 year, 35 %(14 cases) in age group more than 40 years

Table 7: Distribution According to Age Group and Bleeding Pattern

Age	Type of Bleeding						Total
	Acy-clical	Meno-rrhagia	Metro-rrhagia	Oligo-menorrhoea	Poly-menorrhoea	Poly-menorrhagia	
<20	3	10	1	6	1	1	22
21-30	0	12	0	1	2	1	16
31-40	11	24	3	3	5	11	57
>40	6	14	1	3	5	16	45
Total	20	62	5	13	13	27	140

Graph 7: Distribution According to Age Group and Bleeding Pattern

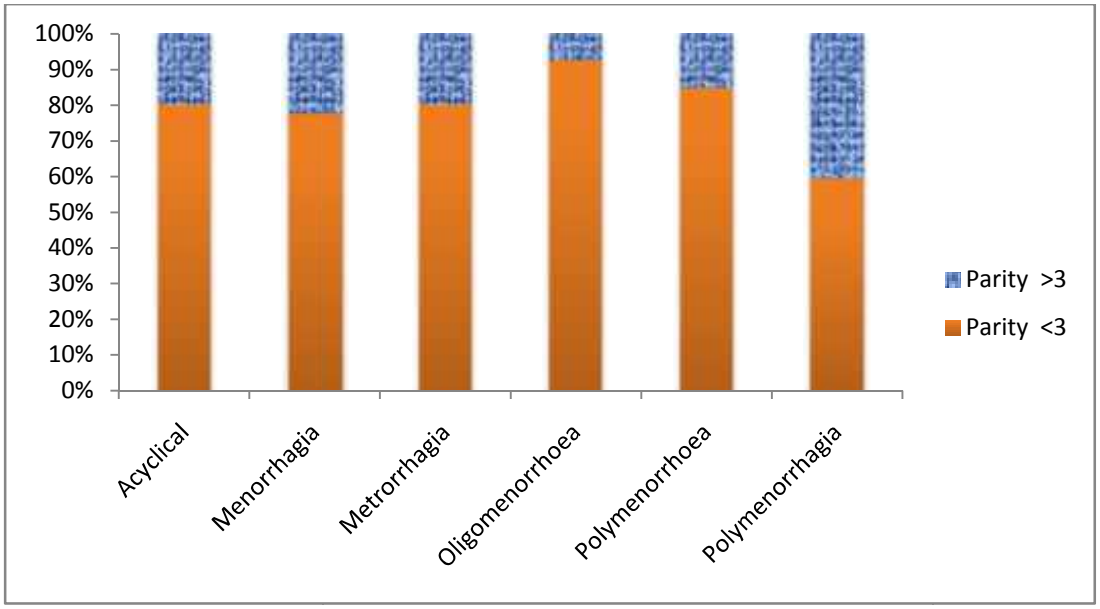


The following table shows the relationship between the parity and type of bleeding pattern. Menorrhagia is the common type of bleeding pattern in both groups of parity, followed by Acyclical and polymenorrhagia in parity less than 3 and in parity more than 3 polymenorrhagia.

Table 8: Distribution according to Parity and Bleeding Pattern

Type of Bleeding	Parity		
	<3	>3	Total
Acyclical	16	4	20
Menorrhagia	48	14	62
Metrorrhagia	4	1	5
Oligomenorrhoea	12	1	13
Polymenorrhoea	11	2	13
Polymenorrhagia	16	11	27
Total	107	33	140

Graph 8: Percent Distribution according to Parity and Bleeding Pattern

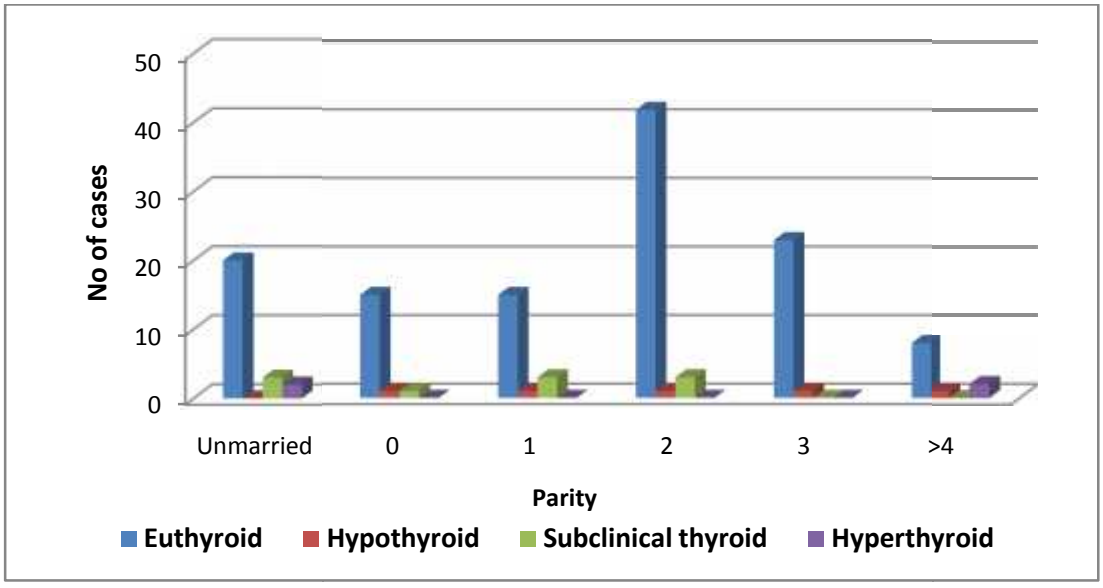


The following table shows the relationship between the parity and incidence of thyroid disorders. In the unmarried group which constituted of 25 patients, 5(20%) patients had thyroid disorders. In the nulliparous group consisting of 17 patients, 2(12%) had thyroid dysfunction. Among 19 para 1 patients who took part in the study, 4(21%) patients had thyroid dysfunction. In the patients who were para 2, out of 46 patients 4(9%) patients had thyroid disorders. In patients who were para 3, out of 24 cases,1(4%) case had thyroid disorder . With parity 4 or more 1(12%) out of 9 cases had thyroid dysfunction.

Table 9: Thyroid Dysfunction in Relation to Parity

Parity	Euthyroid	Hypothyroid	Subclinical thyroid	Hyperthyroid	Total	Percent TDF
Unmarried	20	0	3	2	25	20%
0	15	1	1	0	17	11.7%
1	15	1	3	0	19	21%
2	42	1	3	0	46	8.6%
3	23	1	0	0	24	4.1%
>4	8	1	0	0	9	33%
Total	123	5	10	2	140	100%

Graph 9: Thyroid Dysfunction in Relation to Parity

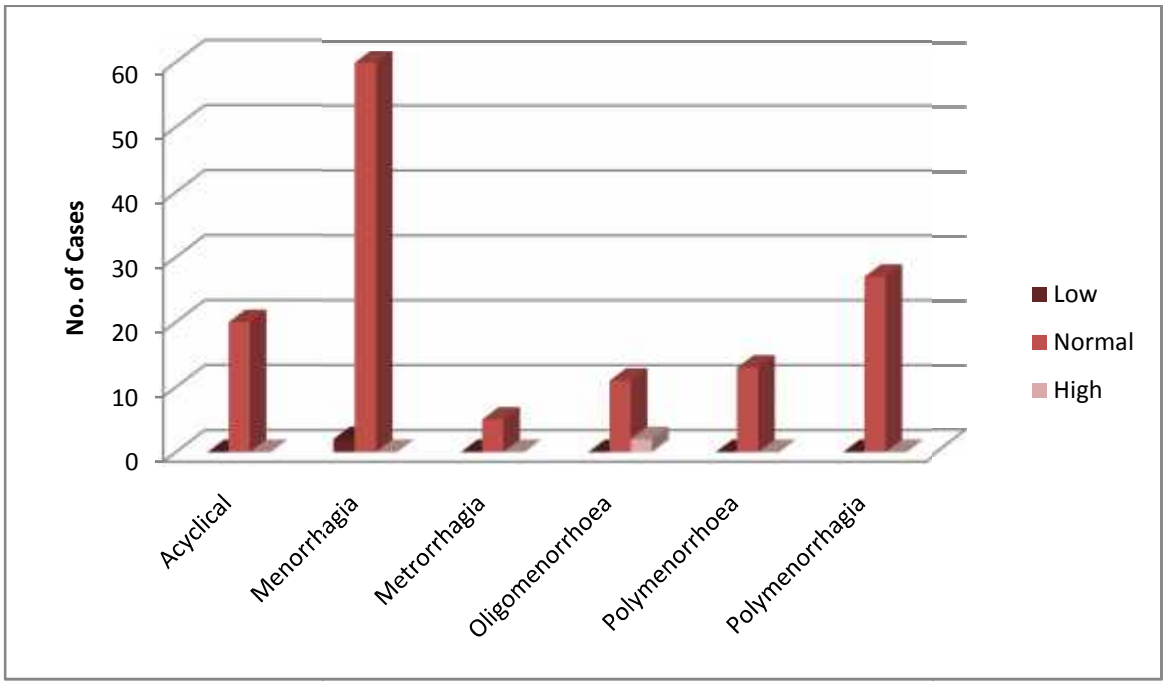


T3 levels of 4 patients out of 17 patients with thyroid disorders were abnormal. 2 patients had low T3 value and 2 patients had higher than normal range. T3 alone appears to be not very sensitive in detecting thyroid disorder.

Table 10: T3 Levels and Bleeding Pattern

T3 level	Type of Bleeding						Total
	Acy-clical	Meno-rrhagia	Metro-rrhagia	Oligo-menorrhoea	Poly-menorrhoea	Poly-menorrhagia	
Low	0	2	0	0	0	0	2
Normal	20	60	5	11	13	27	136
High	0	0	0	2	0	0	2
Total	20	62	5	13	13	27	140

Graph 10: T3 Levels and Bleeding Pattern

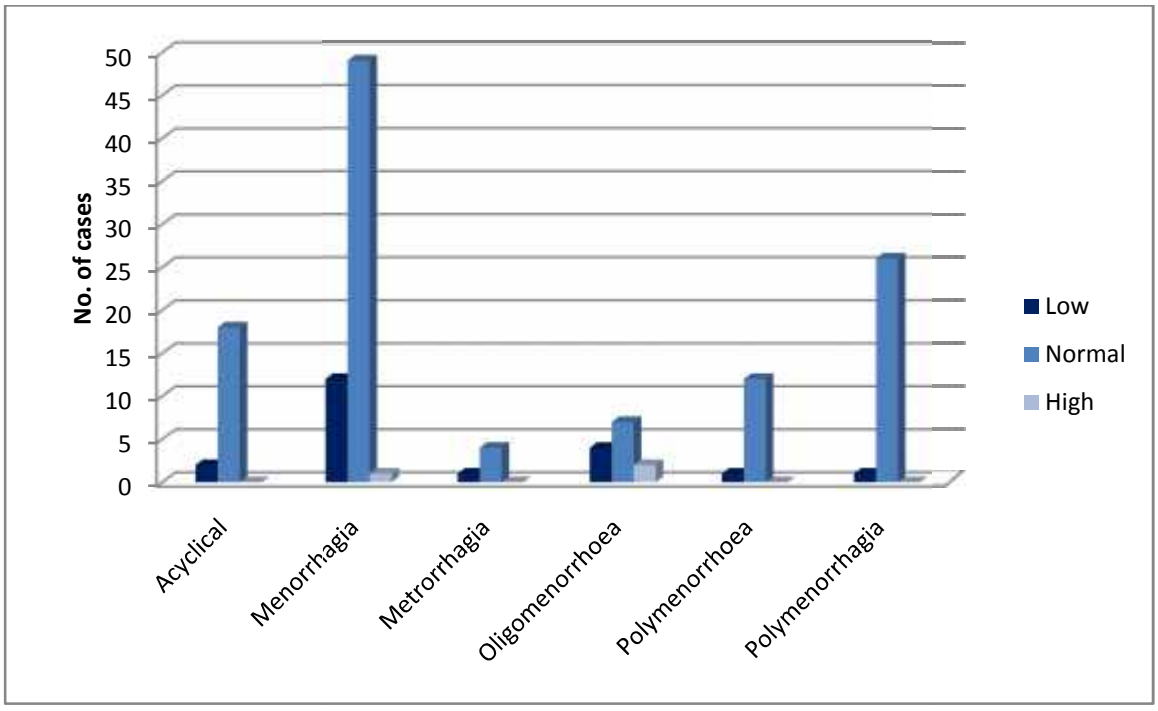


T4 levels were found to be low in 21 cases and the type of commonest bleeding seen was menorrhagia. 3 cases showed elevated T4 levels having oligomenorrhoea as commonest symptom. 26 % of patients presenting with menorrhagia had hypothyroidism and 18 % with oligomenorrhoea had hyperthyroidism

Table 11: T4 Levels and Bleeding Pattern

T4 level	Type of Bleeding						Total
	Acy-clical	Meno-rrhagia	Metro-rrhagia	Oligo-menorrhoea	Poly-menorrhoea	Poly-menorrhagia	
Low	1	1	0	0	0	0	2
Normal	21	56	7	10	14	26	135
High	0	0	0	2	0	0	3
Total	20	62	5	13	13	27	140

Graph 11: T4 Levels and Bleeding Pattern

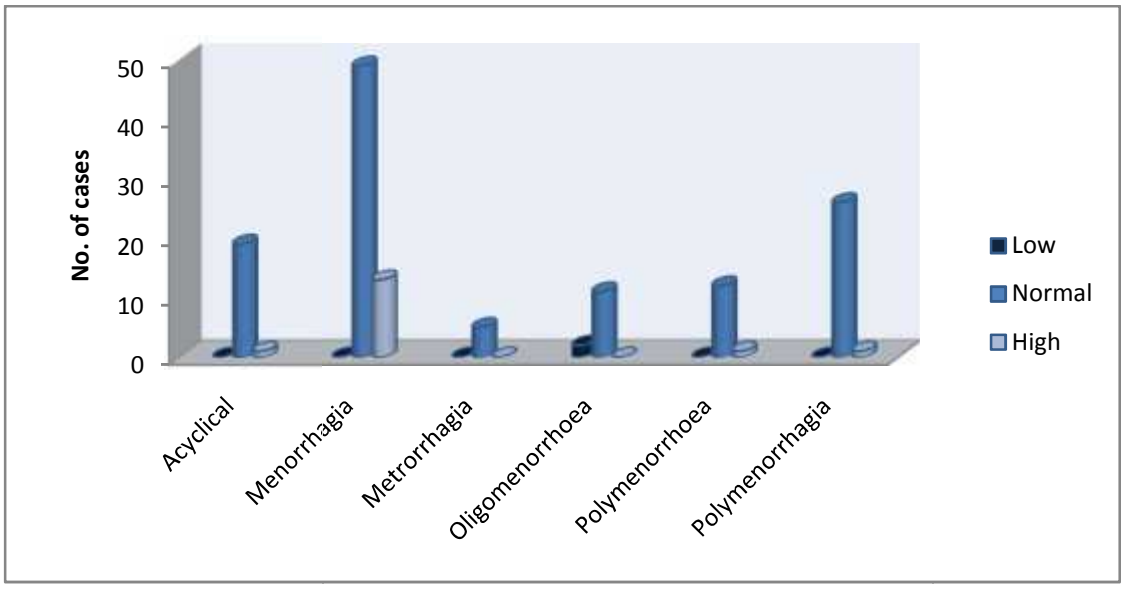


The following table shows that majority of the patients with thyroid dysfunction had the bleeding pattern of menorrhagia (55%). TSH is sensitive in detecting thyroid disorders and 17 cases having thyroid disorders had abnormal TSH values.

Table 12: TSH Levels and Bleeding Pattern

TSH level	Type of Bleeding						Total
	Acy-clical	Meno-rrhagia	Metro-rrhagia	Oligo-menorrhoea	Poly-menorrhoea	Poly-menorrhagia	
Low	0	0	0	2	0	0	2
Normal	19	52	5	11	12	26	125
High	1	10	1	0	1	2	15
Total	20	62	6	13	13	28	140

Graph 12: TSH Levels and Bleeding Pattern



The following table shows out of 17 patients with thyroid disorder 8 of them had significantly raised anti TPO antibody levels detecting autoimmune thyroid disease. And most of them showed menorrhagia as a common bleeding pattern

Table 13: TPO Ab Levels and Bleeding Pattern

TPO level	Type of Bleeding						Total
	Acyclical	Menorrhagia	Metrorrhagia	Oligomenorrhoea	Polymenorrhoea	Polymenorrhagia	
Normal	20	54	5	13	1	12	132
High	1	6	0	0	0	1	8
Total	21	60	5	13	1	13	140

Graph 13: TPO Ab Levels and Bleeding Pattern

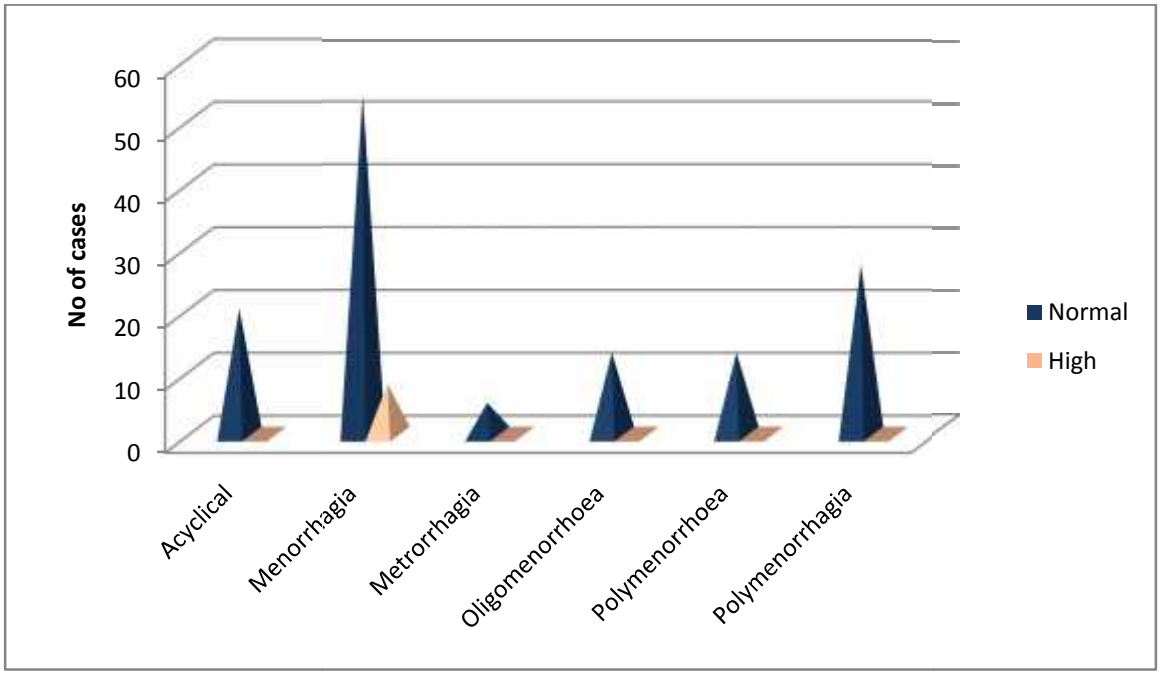
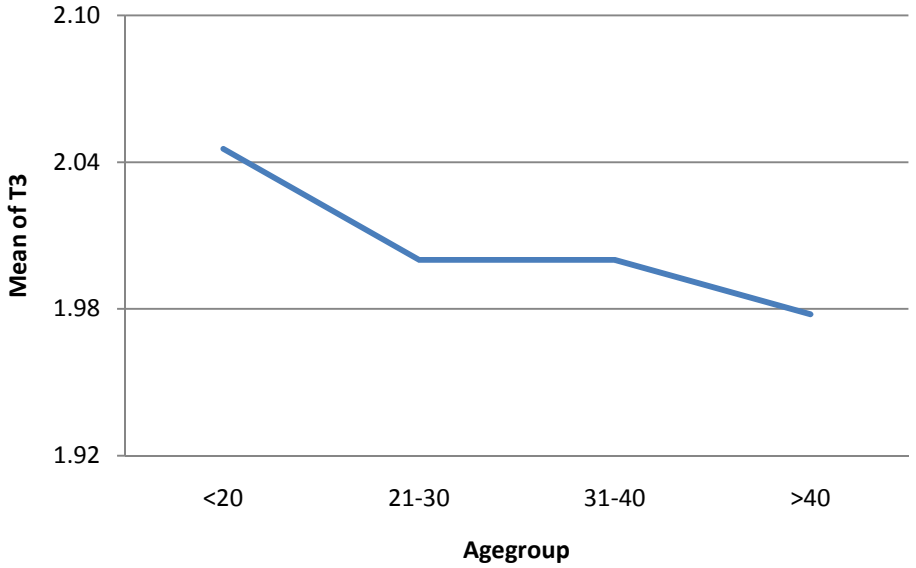


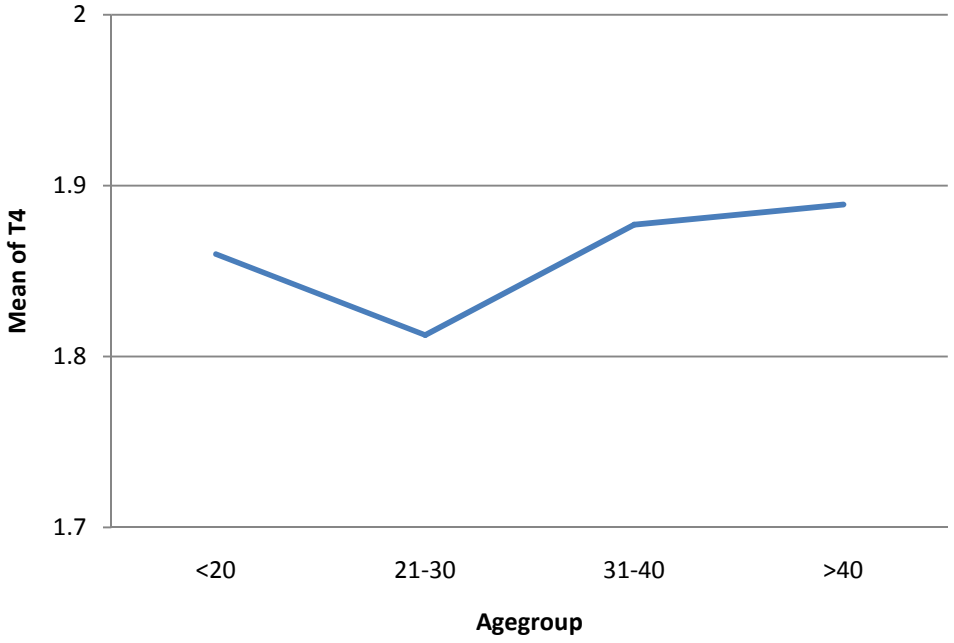
Table 14: Distribution of T3, T4, TSH and TPO Ab Levels with age group by grouped means

Age	No. of cases	T3		T4		TSH		TPO Ab	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
<20	22	2.05	0.38	1.86	0.56	2.00	0.44	1.09	0.29
21-30	16	2.00	0.00	1.81	0.40	2.19	0.40	1.06	0.25
31-40	57	2.00	0.00	1.88	0.38	2.12	0.33	1.05	0.23
>40	45	1.98	0.15	1.89	0.32	2.09	0.29	1.04	0.21
Total	140	2.00	0.17	1.87	0.39	2.10	0.35	1.06	0.23

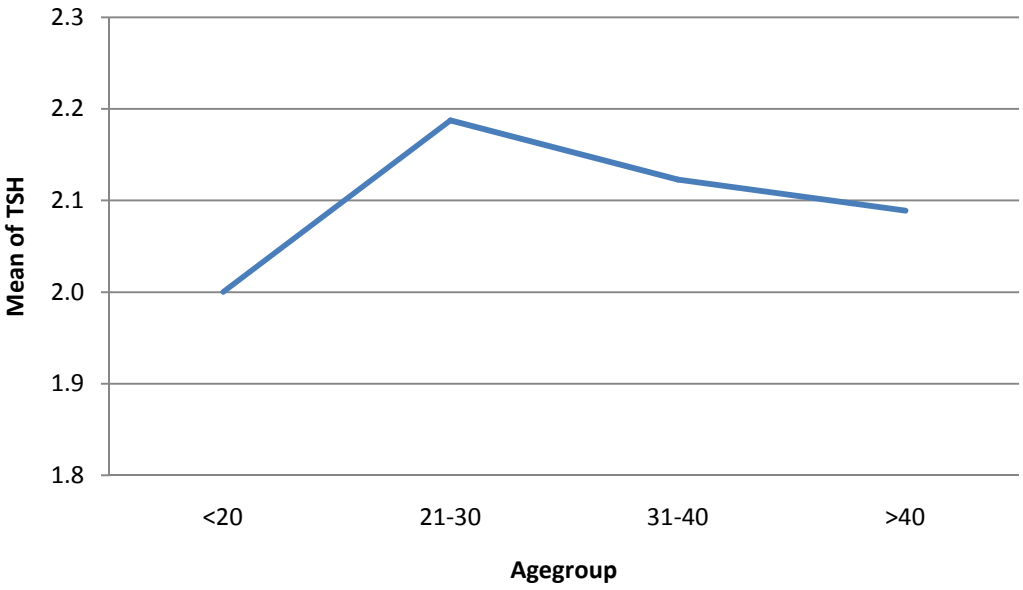
Graph 14.1: Mean value of T3 with age group



Graph 14.2: Mean value of T4 with age group



Graph 14.3: Mean value of TSH with age group



Graph 14.4: Mean value of TPO with age group

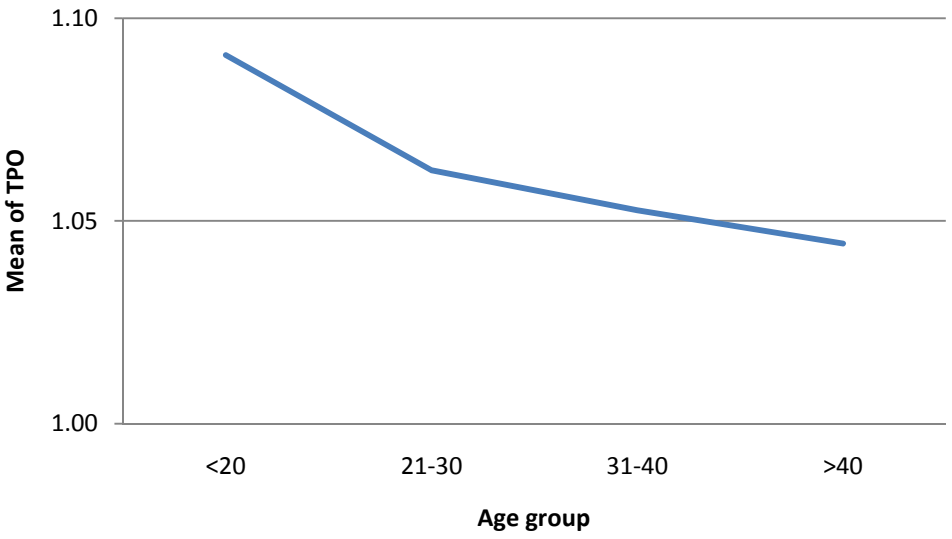


Table 15: One-way ANOVA for T3, T4 & TSH between Age Groups

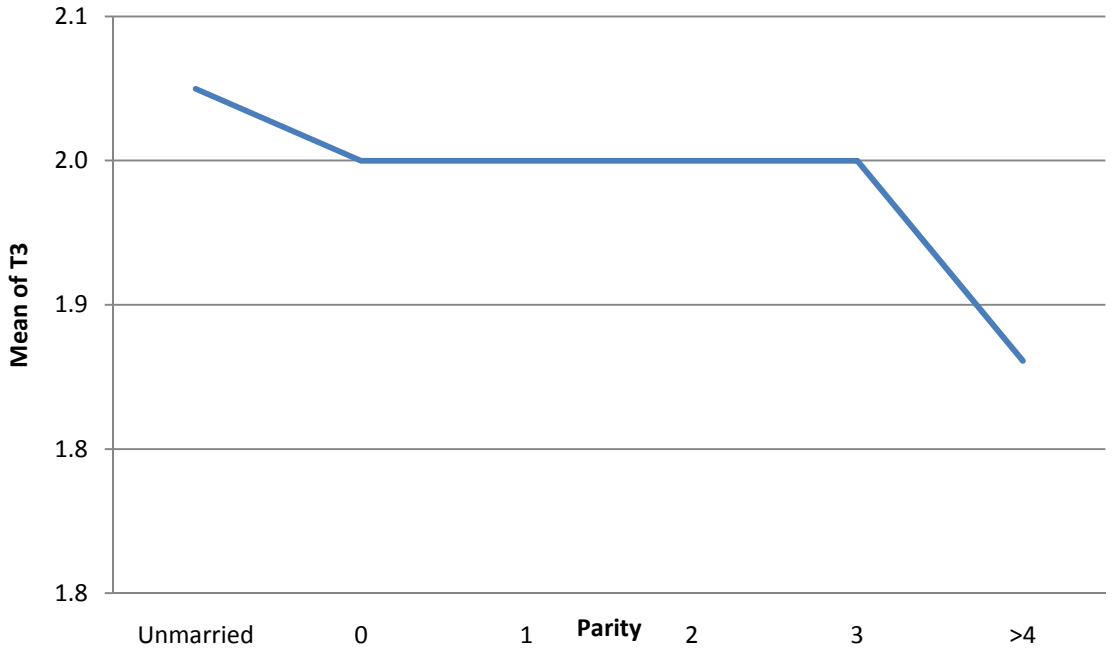
Treatments	Source of error	Sum of Squares	df	Mean Square	F	p value
T3	Between Groups	0.068	3	0.023	0.78	0.507
	Within Groups	3.932	136	0.029		
	Total	4	139			
T4	Between Groups	0.073	3	0.024	0.152	0.928
	Within Groups	21.613	136	0.159		
	Total	21.686	139			
TSH	Between Groups	0.378	3	0.126	1.055	0.37
	Within Groups	16.222	136	0.119		
	Total	16.6	139			
TPO	Between Groups	0.034	3	0.011	0.205	0.893
	Within Groups	7.509	136	0.055		
	Total	7.543	139			

There is no statistically significant variation of T3, T4, TSH & TPO across the age groups

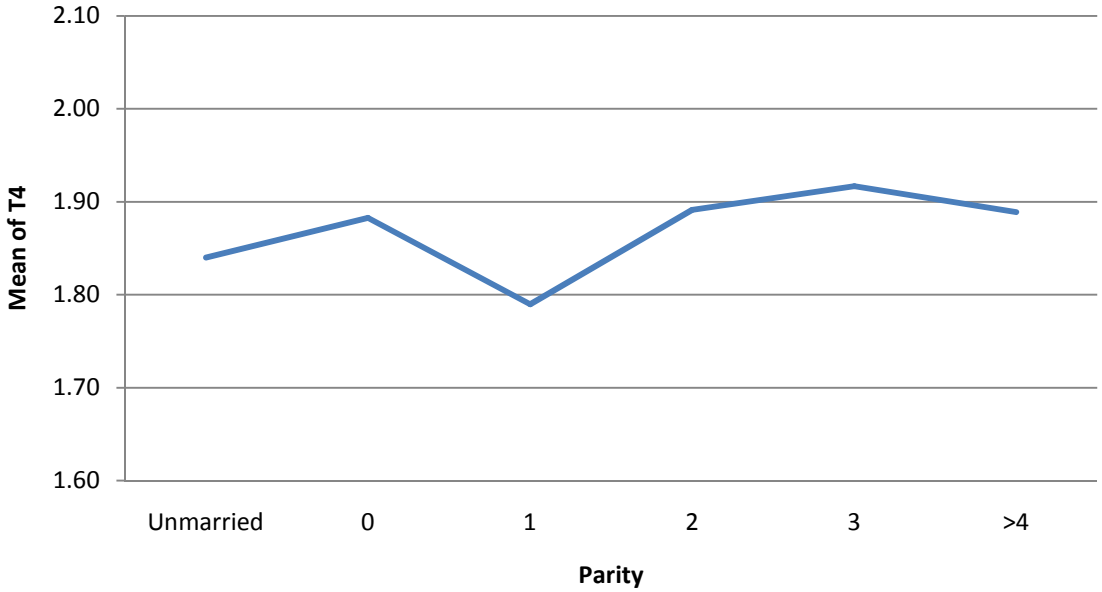
Table 16: Distribution of T3, T4, TSH and TPO Ab Levels with parity by grouped means

Parity	Number of cases	T3		T4		TSH		TPO Ab	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Unmarried	25	2.04	0.35	1.84	0.55	2.04	0.45	1.08	0.28
0	17	2.00	0.00	1.88	0.33	2.12	0.33	1.06	0.24
1	19	2.00	0.00	1.79	0.42	2.21	0.42	1.16	0.37
2	46	2.00	0.00	1.89	0.38	2.09	0.28	1.02	0.15
3	24	2.00	0.00	1.92	0.28	2.04	0.20	1.00	0.00
>4	9	1.89	0.33	1.89	0.33	2.22	0.44	1.11	0.33
Total	140	2.00	0.17	1.87	0.39	2.10	0.35	1.06	0.23

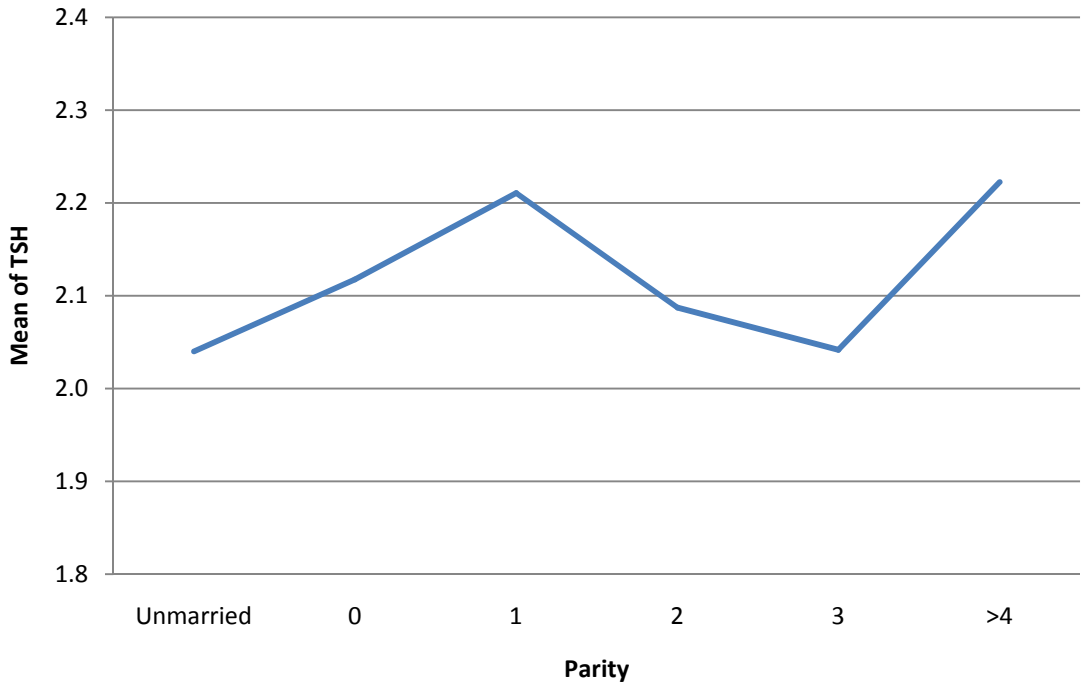
Graph 16.1: Mean value of T3 with Parity



Graph 16.2: Mean value of T4 with Parity



Graph 16.3: Mean value of TSH with Parity



Graph 16.4: Mean value of TPO with Parity

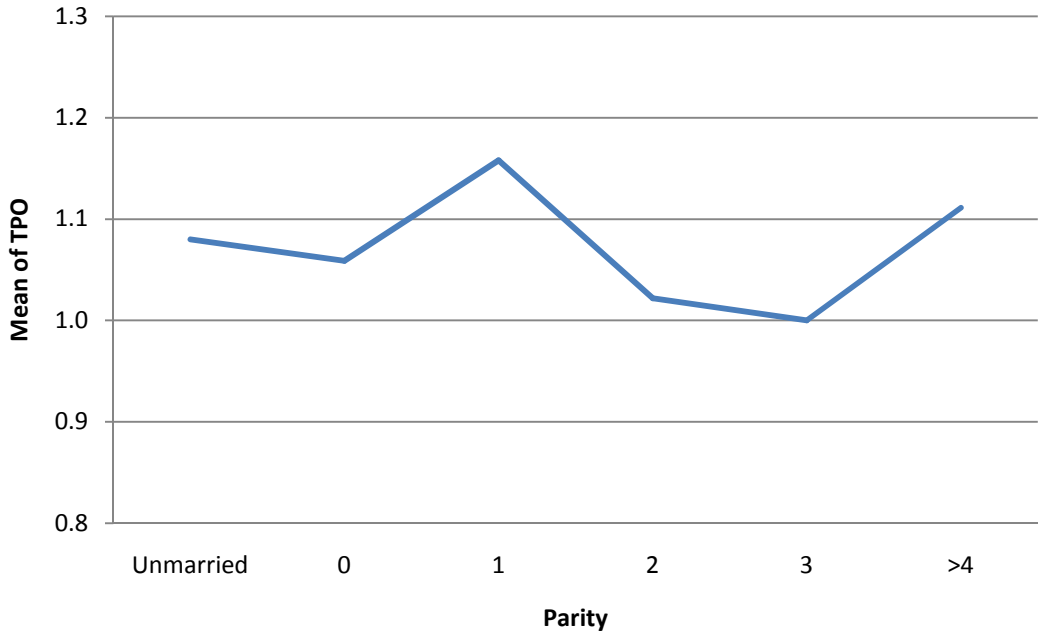


Table 17: One-way ANOVA for T3, T4 & TSH between parity

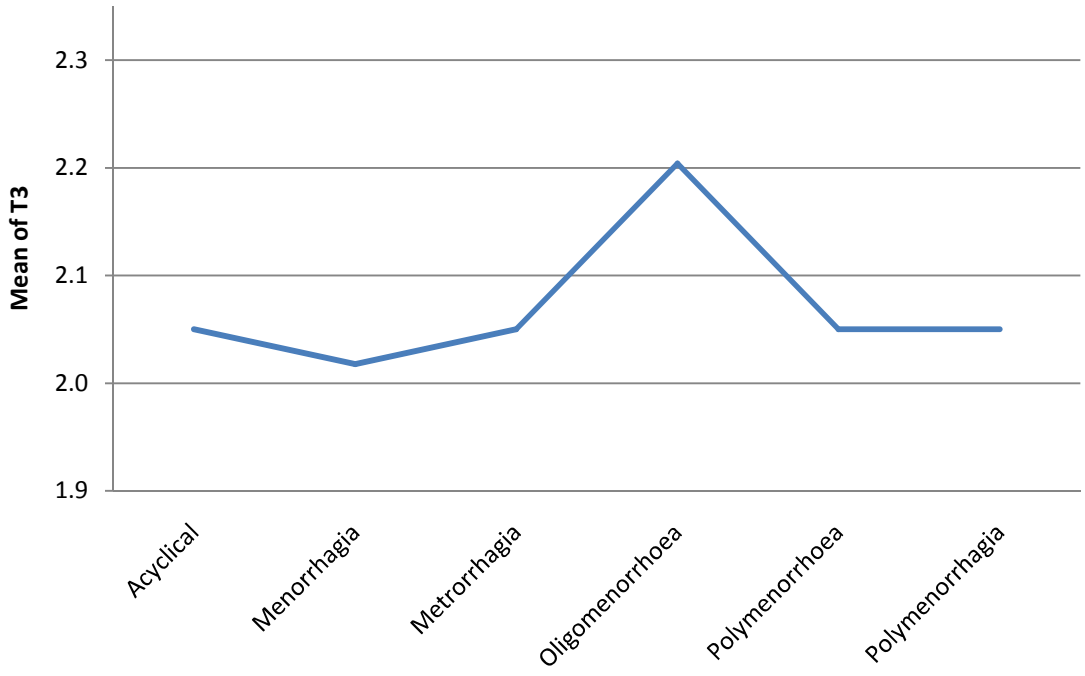
Treatments	Source of error	Sum of Squares	df	Mean Square	F	p value
	Between Groups	0.151	5	0.03	1.052	0.39
	Within Groups	3.849	134	0.029		
T3	Total	4	139			
	Between Groups	0.224	5	0.045	0.28	0.923
	Within Groups	21.461	134	0.16		
T4	Total	21.686	139			
	Between Groups	0.551	5	0.11	0.921	0.47
	Within Groups	16.049	134	0.12		
TSH	Total	16.6	139			
	Between Groups	0.368	5	0.074	1.375	0.237
	Within Groups	7.175	134	0.054		
TPO	Total	7.543	139			

There is no statistically significant variation of T3, T4, TSH & TPO across the parity

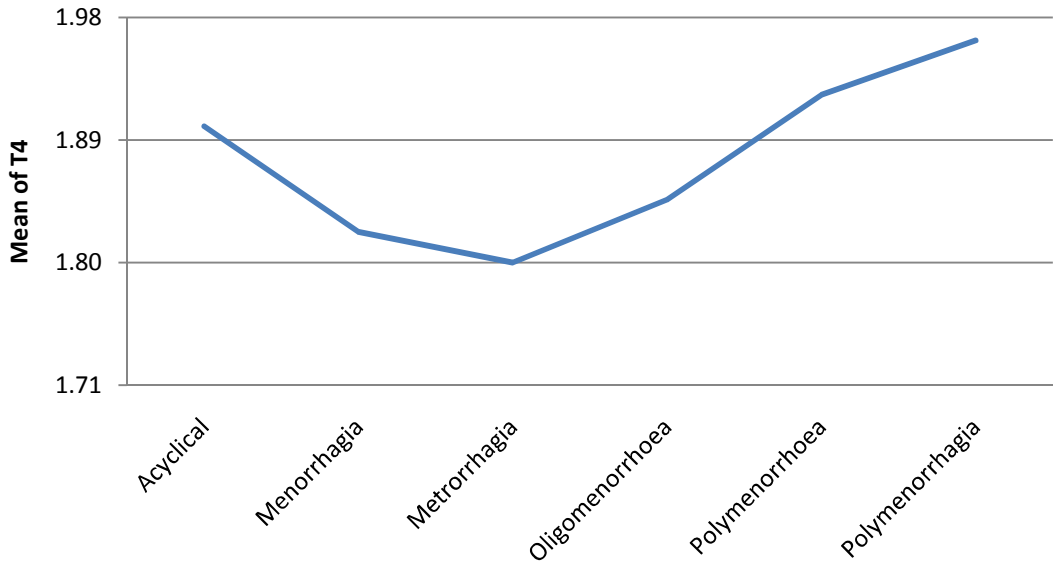
Table 18: Distribution of T3, T4, TSH and TPO Ab Levels with Dysfunctional uterine bleeding by grouped means

Bleeding Type	No of cases	T3		T4		TSH		TPO Ab	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Acyclical	20	2.00	0.00	1.90	0.31	2.05	0.22	1.00	0.00
Menorrhagia	62	1.97	0.18	1.82	0.43	2.21	0.41	1.13	0.34
Metrorrhagia	5	2.00	0.00	1.80	0.45	2.00	0.00	1.00	0.00
Oligomenorrhoea	13	2.15	0.38	1.85	0.69	1.85	0.38	1.00	0.00
Polymenorrhoea	13	2.00	0.00	1.92	0.28	2.08	0.28	1.00	0.00
Polymenorrhagia	27	2.00	0.00	1.96	0.19	2.04	0.19	1.00	0.00
Total	140	2.00	0.17	1.87	0.39	2.10	0.35	1.06	0.23

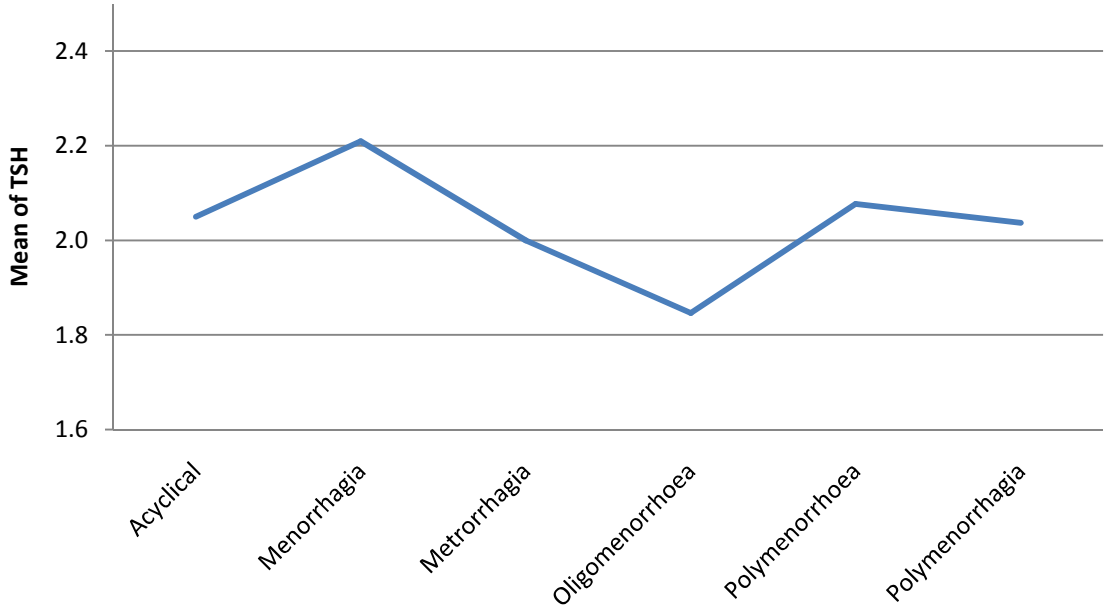
Graph 18.1: Mean value of T3 with Dysfunctional uterine bleeding



Graph 18.2: Mean value of T4 with Dysfunctional uterine bleeding



Graph 18.3: Mean value of TSH with Dysfunctional uterine bleeding



Graph 18.4: Mean value of TPO with Dysfunctional uterine bleeding

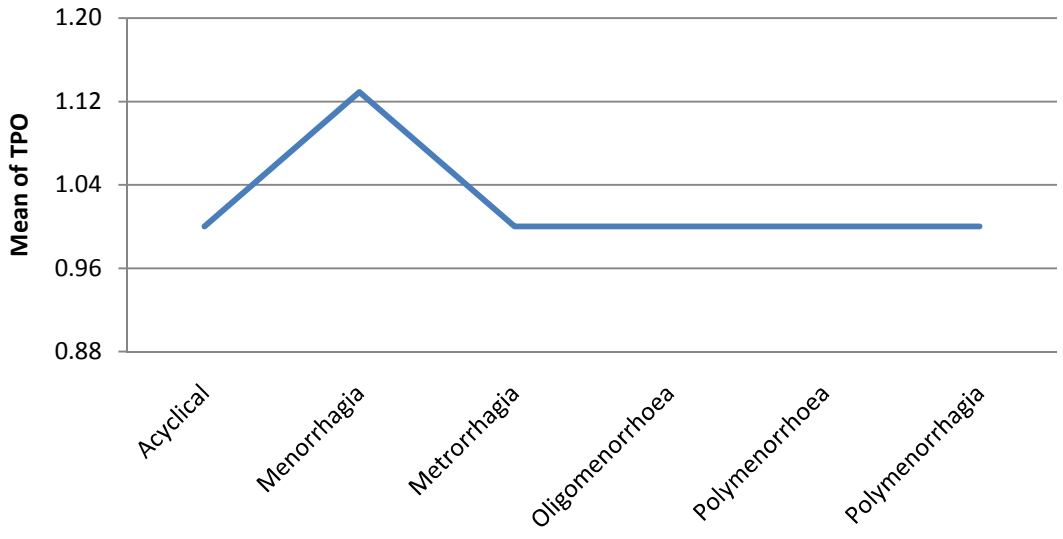


Table 19: One-way ANOVA for T3, T4 & TSH between Dysfunctional uterine bleeding

Treatments	Source of error	Sum of Squares	df	Mean Square	F	p value
T3	Between Groups	0.372	5	0.074	2.75	0.021
	Within Groups	3.628	134	0.027		
	Total	4	139			
T4	Between Groups	0.459	5	0.092	0.579	0.716
	Within Groups	21.227	134	0.158		
	Total	21.686	139			
TSH	Between Groups	1.797	5	0.359	3.254	0.008
	Within Groups	14.803	134	0.11		
	Total	16.6	139			
TPO	Between Groups	0.575	5	0.115	2.212	0.057
	Within Groups	6.968	134	0.052		
	Total	7.543	139			

The variation of mean T3 across categories of Dysfunctional uterine bleeding is statistically significant at 5% level of significance.

The variation of mean TSH across categories of Dysfunctional uterine bleeding is highly statistically significant at 1% level of significance.

The variation of mean TPO across categories of Dysfunctional uterine bleeding is also statistically significant at 10% level of significance.

DISCUSSION

The following is a comparison of distribution of patients according to the age group of the authors study with the present study.

Compared to Authors study in the present study the percentage of patients with thyroid dysfunction in the age group below 20 years is 22.22 % V/s 11.67 %. In the authors study the percentage of thyroid abnormalities in the age group of 21-30 years is 16.67 % in our study it is 23.07 %. The percentage of patients in 31-40 years of age group in 11.76 % in our study and in the author's study it is 48.33 %.

Table 20 :Age Pattern in DUB with Thyroid Dysfunction

Age in years	Present study		Authors Study (C.D. Doifode et al., 2001)	
	No. Of Patients with TOF	%	No. Of Patients with TOF	%
< 20 Years	4/18	22.22	7	11.67
21-30 Years	3/13	23.07	10	16.67
31-40 Years	6/51	11.76	29	48.33
> 40 Years	4/41	9.75	14	23.33

In the authors study majority of the patients who had thyroid dysfunction belonged to the para 1. In the present study, majority of the cases with thyroid dysfunction has parity of 4 or more.

Table 21 : Dysfunction in Relation to Parity

Parity	Present study		Authors Study (C.D. Doifode et al., 2001)	
	No. of Patients with TOF	%	No. of Patients with TOF	%
Unmarried	5	20	9	15
0	2	12	4	6.67
1	4	21	20	33.33
2	4	9	9	15
3	1	4	12	20
4 and above	1	33	6	10

In the present study the incidence of hypothyroidism both (subclinical and clinical) is 11%. In the Authors Study (C.D. Doifode et al., 2001) the incidence was 28.17%.

Table 22 : Hypothyroidism in Different Bleeding Patterns

Study	No. of Patients with menorrhagia, polymenorrhagia, metrorrhagia, acyclical	Patients who had Hypothyroidism	
		No. of Cases	Percentage
Present study	140	15	10.71
Authors Study (C.D. Doifode et al., 2001)	213	60	28.17

Comparing the menstrual pattern in the present study and the authors study, 13% has acyclical types of bleeding in the present study and only 7% of patients had acyclical pattern in the authors study. The maximum patients had menorrhagia 66.66% in the present study, this correlates with the authors study, where 63.33% had menorrhagia. Polymenorragia was seen in 6.66% of the patient in the present study in authors study 23.33% of patients with hypothyroidism.

Table 23 : Menstrual Pattern in Hypothyroid Patients

Bleeding pattern	Our study		Authors Study (C.D. Doifode et al., 2001)	
	No. Of Cases	%	No. Of Cases	%
Acyclical	2/15	13.33	4	6.66
Menorrhagia	10/15	66.66	38	63.33
Polymenorrhagia	1/15	6.66	14	23.33
Metrorragia	1/15	6.66	11	6.66
Oligomenorrhoea	-	-	-	-
Polymenorrhoea	1/15	6.66	-	-

In the present study the prevalence of subclinical hypothyroidism in menorrhagic patients is 12.9%. In the authors study the prevalence of sub clinical hypothyroidism in patients with complaints of menorrhagia is 22.3%.

Table 24 : Sub Clinical Hypothyroidism in Menorrhagic Patients

Study	Sub Clinical Hypothyroid Cases in Menorrhagic Patients	Percentage
Authors Study (C.D. Doifode et al., 2001)	15	22.3%
Our Study	8	12.9%

In the present study, in the patients of age group below 20 years with complaints of menorrhagia 20% (2/10) had sub-clinical hypothyroidism. In the authors study 4.2% had sub-clinical hypothyroidism and 2.8% had hypothyroidism.

Table 25 : Hypothyroidism in Menorrhagia cases < 20 years of age

Study	Sub Clinical Hypothyroidism	Hypothyroidism
Authors Study (C.D. Doifode et al., 2001)	4.2%	2.8%
Our Study	20%(2/10)	-

In the authors study 80% of cases with oligomenorrhoea had hypothyroidism. In our present study 15.38% of cases with oligomenorrhoea (2/13) had thyroid disorder hyperthyroidism.

Table 26 : Oligomenorrhoea and Thyroid Dysfunction

Study	Cases	Hypothyroidism	%	Hyperthyroidism	%	Total % of Thyroid Dysfunction
Authors Study (C.D. Doifode etal., 2001)	10	8	80.0	-	-	80.0
Our Study	13	-	-	2	15.38	15.38

SUMMARY

The present study included 140 cases who were clinically diagnosed as DUB, who presented to our hospital with various menstrual complaints. The study was aimed to evaluate and detect thyroid dysfunction in patients with dysfunctional uterine bleeding (belonging to all age group), most importantly in menorrhagic patients.

Also the study aimed to detect thyroid dysfunction in these patients and treat them medically by referring them to a physician in order to avoid surgery unnecessarily.

- In the patient study, maximum patients belonged to the age group of more than 40 years, 45 patients accounting for 32%. - The most common bleeding patients seen among the 140 cases was menorrhagia. 44% of patients had menorrhagia. - The least common bleeding pattern (4%) was metrorrhagia.- Maximum patients in the study belongs to para 2 (33%) minimum were having parity of 4 or more (6%).
- 88% of patients who took part in the study had euthyroid status.
- 12% of patients from the present study were noted to have thyroid dysfunction.
- Maximum patients diagnosed to have thyroid dysfunction had subclinical hypothyroidism (10 cases).
- 4% of the patients from the study had hypothyroidism.
- 1% had hyperthyroidism.
- Thyroid dysfunction was commonest in age group 31-40 and above 40 years.

- Patients who presented with menorrhagia had 44% prevalence of thyroid disorders. Hence this appears to be the most common bleeding pattern to be associated with thyroid disorder.
- Patients who presented with polymenorrhagia has 19.3% prevalence of thyroid disorders.
- The least common association is seen with patients with metrorrhagia, only 3.6% had thyroid disorders.
- In patients who were aged < 20 years, menorrhagia was the most common bleeding pattern (45%).
- In patients aged > 40 years, polymenorrhagia is the most common bleeding pattern (35.5%).
- Subclinical hypothyroidism was the most predominant thyroid dysfunction.
- Maximum patients who had thyroid dysfunction presented with menorrhagia (26%).
- Out of 17 patients who had thyroid function disorder, 4 had abnormal T3 values, and 5 patient had abnormal T4 value.
- TSH appears to be the most sensitive test to evaluate thyroid function.it was abnormal in 97% of cases detected to have thyroid dysfunction.
- Out of 17 patients with thyroid dysfunction, 8 patients showed elevated TPO antibody (47%) suggestive of autoimmune thyroid disorders
- Therefore we summarize that any type of menstrual disorder should be considered as a possible presenting symptom of thyroid dysfunction and it may even indicate subclinical abnormality

CONCLUSION

This study which was done on patients who were provisionally diagnosed with dysfunctional uterine bleeding concludes that.

- There is a high prevalence of thyroid disorders in cases which are clinically diagnosed as DUB.
- Hence the biochemical evaluation of T3, T4, TSH and TPO antibody is extremely important and valuable in detecting these patients.
- Anti-thyroid peroxidase autoantibodies (anti-TPO), considered as the most sensitive and specific marker of thyroid autoimmunity
- The appearance of TPOAb usually precedes the development of thyroid dysfunction
- In patients with subclinical hypothyroidism, the presence of TPO antibodies is associated with an increased risk of developing overt hypothyroidism
- TPO antibody test as a diagnostic tool in deciding whether to treat a patient with subclinical hypothyroidism
- Furthermore, it raises the concern that such patients may be at increased risk of developing other autoimmune diseases.
- Unnecessary surgery was avoided in 12% of patients and they were treated medically which was more accurate and cost effective

Hence thyroid function evaluation should be made mandatory in cases of DUB to detect thyroid dysfunction and these cases should be referred to physician for further medical treatment.

BIBLIOGRAPHY:

1. Davey. DA. Dewhurst. Text book of obstetrics and gynaecology for post graduates. DUB, Chapter 40, 5th Edn; 1990: 590-600.
2. Lakshmi Singh, CG Agarwal, SR Chowdhary, P. Mehra, Rajana Khare. Thyroid profile in infertile women. J. Of Obst. And Gyn of India 1990 ; 40: 248.
3. Douglas L. Wilansky and Bernard Grisesman. Early hypothyroidism in patients with menorrhagia. Am. J. Obst and Gyn. 1989 ; 160 : 613.
4. Rebecca Abraham, V Srinivasa Murugan Et al., : Thyroid disorders in women of puducherry, Indian journal of clinical biochemicstry, 2009 ; 24 : 52-59.
5. Danese MD, Powe NR, Swain CT, Ladenson PW. Screening for mild thyroid failure at the periodic health examination. A decision and Cost effective analysis. JAMA 1996 ; 276: 285.
6. John W. Ely, M.D., MSPH, Colleen M. Kennedy, MD, MS, Elizabeth C. Clark, MD et al., :Abnormal uterine bleeding : A management algorithm. Department of obstetrics and Gynaecology, University of lowa Carver College of Medicine, Lowa City. IA: 1-17
7. Ingbar SH, Wiwams RH. Textbook of endocrinology, 7th edn. 1985: 792.
8. Rosalind Pitt Rivers and WR Trotter. The thyroid gland. 1964:75
9. Scott JC and Mussey E. Menstrual patterns in myxoedema. Am J of Obst & Gyn 1964; 90:161-5.
10. EO Akande. Plasma estrogen in euthyroid and thyrotoxic women. Am J of Obst & Gynaec August 1975; 22(7): 880.

11. Edson TR, et al. Low platelet adhesiveness and other hemostatic abnormalities in hypothyroidism. Am Int Med 1975; 82: 324.
12. Sheldon S. Stoffer, Menstrual disorders and mild thyroid insufficiency.Postgraduate Medicine. August 1982 ; 72 (2).
13. Ivor MD, Jackson. Thyrotropin releasing hormone. New Engl J of Med 1982; 306: 145.
14. Jayadey Mukherjee and NN Roy Chowdhary. A review of 70 cases of puberty menorrhagia. J Obst & Gynaec of India 1986:121.
15. I Ross McDougall. Thyroid diseases in clinical practice. 1st Edn. 1992.
16. Dipak Lahiri, Anian Dasgupta, Sarmila Kundu. Menstrual pattern and fertility status of hypothyroid women. J Obst & Gynaec of India 1996; 47: 663.
17. Leon Speroff. Clinical gynaecologic, endocrinology and infertility. Chapter-15,6th Edn; 1999: 575-590.
18. Charusheela D, Doifode, and Kalpana Fernandes. Study of thyroid dysfunction in patients with dysfunction uterine bleeding. J Obst and Gynaec of India, March 2001 ; 51 (2) : 93-95.
19. Wilansky DL, Greisman B : Early hypothyroidism in patients with menorrhagia, Department of medicine, Etobicoke General hospital, Rexdale, Ontario, Canada. Am. J. of Obstet Gynecol. 1990 Aug ; 163 (2) : 697.
20. JV Joshi, SD Bhandarkar, M. Chandha et al.,Menstrual irregularities and location failure may precede thyroid dysfunction or goitre, Institute of research in reproduction, Seth GS Medical College, Parel, Bombay, Maharashtra, 39 (3) ; 1993 : 137-41.

21. Krassas GE, Pontikides N, Kaltsas, Papadopoulou P, et al., : Distrubances of menstruation in hypothyroidism. Department of endocrinology, Panagia Hospital, Thessaloniki, Greece; 11.
22. Andrew D. Weeks : Evidence supports associations between hypothyroidisms and menorrhagia, BMJ 2000 ; 320 : 649.
23. P.C Kek, S.C. Ho, D.H. Khoo : Subclinical Thyroid Disease, Signapore Med J 2003;44 (1) : 595-600.
24. Hypothyrodism : Thyroid disorders : Merck Manual Professional : 1 – 5.
25. Janet R., Albers. M.D., Sharon K., Hull M.D., et al., Abnormal uterine bleeding, Am. Fam Physician, 15 Apr 2004 ; 69 (8) : 1915-26.
26. George R. Wilson. M.D., R. Whit Curry. J.R. M.D., : Subclinical thyroid diseases, Am. Fam Physician,15 Oct 2005 ; 72 (8) : 1517-24.
27. Villar HC, Saconato H, Valente O, Atallah AN : Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst. Reve. Jul 18 2007 ; (3) : CD003419.
28. Jonathan S. Berek. Novak's gynaecology. 13th Edn. Chapter-13, 2002:366.
29. Neeraja Bhatla. Abnormal and excessive uterine bleeding. Jeffcoates, Principles of gynaecology.Chapter-38;7th Edn. 2008.
30. Kaur T, Aseeja V, Sharma S. Thyroid Dysfunction in Dysfunctional Uterine Bleeding. Webmed Central Obstetrics and Gynaecology. 2011;2(9):2-7.
31. Sharma N, Sharma A. Journal of Medical Education & Research.2012;14(1):14-7.
32. Sinclair D. Clinical and laboratory aspects of thyroid autoantibodies. Ann Clin Biochem. 2006 May;43(3):173-83.

33. Engler H , Riesen WF, Keller B. Anti-thyroid peroxidase (anti-TPO) antibodies in thyroid diseases, non-thyroidal illness and controls. Clinical validity of a new commercial method for detection of anti-TPO (thyroid microsomal) autoantibodies. Clin Chim Acta. Mar 1994 ; 225 (2) : 123-36.
34. Hollowell J, Staehling N, Flanders D, Hannon W, Gunter E, Spencer C Et al. Serum TSH, T4, and Thyroid Antibodies in the United States Population (1988 to 1994): National Health andNutrition Examination Survey (NHANES III). J Clin Endocrinol Metab, February 2002, 87(2):489–99
35. Roti E, Gardini E, Minelli R, Bianconi L, Bravermam L. Prevalenceof Anti Thyroid Peroxidase Antibodiesin Serum in the Elderly: Comparisonwith Other Tests for Anti-ThyroidAntibodies. Clinical Chemistry 1992;38(1)
36. Townsend,Evers, Matton.chapter 36,Sabisten text book of surgery, 18th edition.Brent GA: The molecular basis of thyroid hormone action. N Engl J Med 1994; 331:847-853
37. Brent GA:The molecular basis of thyroid hormone action. N Engl J Med 1994;331:847-53.
38. Spitzweg C, Heufelder AE, Morris JC: Thyroid iodine transport. Thyroid 2000; 10:321-330.
39. Chopra IJ: Nature, source, and relative significance of circulating thyroid hormones. In: Braverman LE, Utiger RE, ed. Werner and Ingbar's The Thyroid, 7th ed. Philadelphia: Lippincott-Raven; 1996:111-124
40. Robins J: Thyroid hormone transplant proteins and the physiology of hormone binding in the thyroid. In: Braverman LE, Utiger RD. The Thyroid: A

Fundamental and Clinical Text, 8th Edn. Philadelphia: Lippincott Williams & Wilkins; 2000:105.

41. Disorders of thyroid gland.chapter 341, Harrison's principles of internal medicine 18th Edn.
42. BR Walker and AD Toft. Davidson's principles and practice of medicine, 19th Edn. 2002:689-704
43. Sutherland A.M. : Functional uterine hemorrhage in puberty and adolescence. Glasgo. Med. Journal, 1953 ; 34 : 496-509.
44. Sutherland A.M. : Functional uterine hemorrhage in pubery and adolescne. A clinical review of the literature since 1938 ; Glasgo. Med. J. 1949 ; 30 : 1-28.
45. Taylor H.B and Chamlian D.C. : J. Obstet and Gynaecol 1970 ; 36 : 659-666.
46. William J. Butler : Normal and abnormal uterine bleeding. Chapter-22, Telende's operative gynaecology, 8th edn., 1996 ; 453-473.
47. Dawn : Menstrual disorders. Drawn's text book of gynaecology and contraceptives. Chapter-7, 12th Edn., Gipidi Box: 177-86.
48. .Baird : Mechanism of menstrual bleeding. Endocrine basis of Menstruion and its disorders. New York : Raven Press, 1985 ; 165-79.
49. Ryan K.J. Berkowitz R.S., Barbiery R.L. : Kistner's gynaecology, Mosby Company, New Delhi, India ; 7th Edn, 2001 : 23-57.
50. Gyton A.C. : Textbook of medical physiology, W.B. Sanders, India. 10^{th} Edn. 2000 ; 899 - 913.
51. Beck W.W., Jr. National Medical Series for Independent Study- Obstetrics and Gynaecology, Third Edition, Williams and Wilkins.USA ,1999 ; 229-39.

52. Treolar AE, Bayton AE, Benn EG et al. Variation of human menstrual cycle throughout reproductive age Int J Fertil 1967;12:77-126
53. Guillebaud J, Bonner J longer though lighter menstrual and inter menstrual bleeding with Cu IUCD compared to inert IUCD. Br. J obstet gynecol 1978;85;707-12.
54. Rybo G, Leman J, Tibblin E : Epidemiology of menstrual blood loss. In : Baird DT, Michie EA (Eds) Mechanisms of Menstrual Bleeding. New York : Raven Press, 1985 ; 90 : 161-65.
55. World Health Organization Report 753, Mechanism of action, safety and efficacy of intrauterine devices, Geneva : World Health Organization, 1987 ; 56.
56. Hallberg L, Hoegdahl A, Nilsson L et al : Menstrual blood loss – a population study. Acta Obstet Gynecol Scan 1966 ; 45 : 320-51.

ANNEXURES

ETHICAL CLEARANCE

Institutional Ethical Committee
BIJAPUR-586 103.
OUTWARD
No. 466/2
Date 18/10/12
BLDE U's Shri B.M. Patil Medical College

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 18-10-2012 *at* 3-30pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title "Study of thyroid dysfunction in patients with dysfunction uterine bleeding"

Name of P.G. student Dr. Ashwini G. Patil
OBGY.

Name of Guide/Co-investigator Dr V. R. Gobbur.
Prof of OBGY

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

SAMPLE INFORMED CONSENT FORM

TITLE OF THE TOPIC : **"STUDY OF THYROID DYSFUNCTION IN PATIENTS WITH DYSFUNCTIONAL UTERINE BLEEDING"**

PRINCIPAL INVESTIGATOR : Dr. ASHWINI .G.PATIL

PG GUIDE NAME : Dr. VIJAYA LAKSHMI. R. GOBBUR

PURPOSE OF RESEARCH

To know the prevalence of hypothyroidism in patients with DUB and treat medically and avoid surgery

PROCEDURE

I understand that I will be a part of this study. My history and physical findings will be taken from the case paper and will be evaluated in a systematic way. I will not be asked for any follow up.

RISK AND DISCOMFORTS

I understand that this procedure is not expected to aggravate any side effect or cause

BENEFITS

This study is to evaluate the thyroid function in patients having abnormal menstrual bleeding from puberty to premenopausal age groups which will be interesting and justifiable and will help in further management of DUB and also know the prevalence of hypothyroidism in patients provisionally diagnosed as DUB.

CONFIDENTIALITY

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality and privacy regulation of BLDE University's Shri .B. M .Patil Medical college. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting names to numbers will be kept in a secured location**.**

If the data are used for publication in the medical literature or for teaching purpose no names will be used**.**

I understand that the relevant designated authority and permitted to have an access to my medical record and to the data produced by the study for audit purpose. However, they are required to maintain confidentiality**.**

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr Ashwini.G.Patil has explained to me the purpose of research, the study procedure, that I will undergo and the possible discomforts as well as benefits that I may experience in my own language. I have been explained all the above in detail in my own language and I understand the same . Therefore I agree to give consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(witness to signature) Date

PROFORMA

STUDY OF THYROID DYSFUNCTION IN PATIENTS

WITH A PROVISIONAL DIAGNOSIS OF DUB

SERIAL NO: HOSPITAL NO. :

NAME : OCCUPATION :

AGE:

ADDRESS:

SOCIO- ECONOMIC STATUS :

1. CHIEF COMPLAINTS :

2. HISTORY OF PRESENTING COMPLAINTS :

A) Beeding per Vagina :

Duration :

Interval :

Quantity : Scanty / Moderate /Excessive

H/o Dysmenorrhoea : Yes /No

B) Other complaints :

3. MENSTRUAL HISTORY :

Menorrhagia	:	Yes /No
Hypomenorrhoea	:	Yes /No
Metrorrhagia	:	Yes /No
Oligomenorrhoea	:	Yes /No
Polymenorrhagia	:	Yes /No
Polymenorrhoea	:	Yes /No

Age of attainment of menarche:

Previous Menstrual cycles-

- Duration of Cycles :
- Amount of flow :
- Duration of flow :
- Associated dysmenorrhoea:

Date of last menstrual period :

4. OBSTETRIC HISTORY :

Married Life:	Para :	Living :
Abortion :	Last Delivery:	
Type of Deliveries:	Tubectomy :	Yes / No

5. PAST HISTORY :

TB / Bronchial asthma/ Diabetes mellitus / Hypertension/ RHD/Blood transfusion / Thyroid disorders/Any operations.

6. FAMILY HISTORY :

TB / Bronchial Asthma / Diabetes mellitus / Hypertension / Any cancer / Bleeding disorders /

Thyroid disorders

7. PERSONAL HISTORY :

Diet :

Appetite:

Bowels:

Micturation :

Sleep:

Cold & Heat intolerance:

8. GENERAL PHYSICAL EXAMINATION OF PATIENT:

1. Head to toe
    a. Distribution of hair
    b. Thickening of skin : Dryness / scaling
    c. Edema
    d. Hoarseness of voice
2. Nutritional Status
3. Pallor
4. Tremours
5. Thyroid

VITALS:

1. Temperature
2. Pulse rate
3. Blood Pressure
4. Respiratory rate

9. SYSTEMIC EXAMINATION

1. CVS

2. Respiratory system

3. Per Abdomen:

Operative scar : Present / Absent

Engorged vein : Present / Absent

Ascites : Present / Absent

Any enlargement of Liver / Spleen : Palpable / Non Palpable

10. VULVO VAGINA EXAMINATION: Healthy / Non Healthy

11.PER SPECULUM EXAMINATION:

Vagina :

Cervix :

Bleeding : Present / Absent

12.PER VAGINAL EXAMINATION:

Cervix : Normal	☐	Flushed with vault	☐		
Uterus : Anteverted	☐	Retroverted	☐		
Normal size	☐	Bulky	☐	smaller	☐
Soft	☐	Firm	☐	Hard	☐
Mobile	☐	Fixed	☐		

Tender ☐ Non Tender ☐

Tenderness in fornix : Present ☐ Absent ☐

Uterocervical length :

13.PER RECTAL EXAMINATION :

14.INVESTIGATIONS :

- Hb % Platelet count TC, DC
- Urine : Albumin: Sugar: Microscopy:
- BT, CT
- USG abdomen pelvis

15. COMPULSORY :

Thyroid Function Tests :

T3

T4

TSH

TPO ANTIBODY

16. OPTIONAL :

Pap Smear

Histopathology of Endometrium

Hysteroscopy

RESULT :

KEY TO MASTER CHART

Sl. No.	: Serial Number
OPD NO	: Out Patient Dept Number
Inter	: Interval
Dys	: Dysmenorrhoea
LMP	: Last menstrual period
TPOAB	: Thyroid Peroxidase Antibody
TSH	: Thyroid stimulating hormone
+	: Positive
-	: Negative
USG	: Ultrasonography
N	: Normal
Un	: unmarried
Dura	: duration in months

MASTER CHART

sl no	OPD No	Name	Age	Para	Duration	Inter	Dys	LMP	Type of Bleeding	Type of bleeding	T3	T4	TSH	TPO Ab	Euthyroid	hypothyroid	subclinical hypothyroid	hyperthyroid	USG
1	42909	MAHADEVI	23	UN	2	30	+	15	Menorrhagia	2	0.78	8.21	4.91	4.16	+	-	-	-	N
2	43073	GEETA	35	1	4	15	-	10	Polymenorrhoea	5	1.34	6.48	3.75	0.81	+	-	-	-	N
3	39922	ASHA	38	2	6	30	-	15	Menorrhagia	2	1.20	5.07	2.87	4.12	+	-	-	-	N
4	43778	PARVATHI	43	2	8	25-40	-	30	Acyclical	1	1.86	11.41	2.81	0.91	+	-	-	-	N
5	43319	KAMALABAI	27	0	6	30.35	+	45	Menorrhagia	2	0.72	4.95	3.19	2.82	+	-	-	-	N
6	42977	ROBILA	43	2	4	20	-	15	Polymenorrhoea	5	0.81	3.98	8.9	3.93	-	-	+	-	N
7	43335	ASHABAI	45	3	12	28-30	-	10	Menorrhagia	2	1.24	5.97	1.82	1.38	+	-	-	-	N
8	43837	PRIYANKA	37	2	18	15-20	-	12	Polymenorrhagia	6	1.86	4.98	0.91	1.81	+	-	-	-	N
9	42942	SUREKHA	47	6	12	35	+	5	Menorrhagia	2	0.41	3.99	18.98	9.18	-	+	-	-	N
10	43539	BOWAMMA	41	0	4	20-22	-	30	Polymenorrhagia	6	0.86	7.93	1.81	2.48	+	-	-	-	N
11	43332	AKSHANA	16	0	4	40-60	-	5	Acyclical	1	0.97	8.91	0.77	4.17	+	-	-	-	N
12	44358	PRABHAVATI	31	1	3	20	-	10	Polymenorrhagia	6	0.82	5.71	4.32	0.91	+	-	-	-	N
13	36282	RENUKABAI	43	2	8	30	+	15	Menorrhagia	2	0.58	3.10	15.12	4.08	-	+	-	-	N
14	43754	ASHWINI	31	1	6	15-20	+	20	Polymenorrhagia	6	0.92	8.80	0.91	1.18	+	-	-	-	N
15	42979	SHOBHA	45	2	12	30	-	5	Menorrhagia	2	0.67	7.24	4.27	2.62	+	-	-	-	N
16	43829	PUSHPA	25	0	2	20-22	-	10	Polymenorrhoea	5	0.81	8.13	0.82	1.08	+	-	-	-	N
17	43077	ANUJAYA	36	2	3	45-60	-	15	Acyclical	1	0.74	4.84	1.09	0.99	+	-	-	-	N
18	43037	RADIKA	46	6	14	15	+	10	Polymenorrhagia	6	0.93	6.74	2.82	3.43	+	-	-	-	N
19	43063	BHARATI	18	UN	1	30	+	18	Menorrhagia	2	0.87	5.90	3.04	4.23	+	-	-	-	N
20	43057	KALAVATI	31	UN	3	15-20	-	40	Polymenorrhagia	6	0.62	7.50	2.91	4.23	+	-	-	-	N
21	42922	SHIVAMMA	37	2	12	35	-	20	Menorrhagia	2	1.24	8.19	0.98	1.22	+	-	-	-	N
22	42980	LALITHA	33	2	4	20-40	+	10	Metrorrhagia	3	1.82	9.16	3.14	0.71	+	-	-	-	N
23	43429	SHRIDEVI	40	3	18	20-60	-	5	Acyclical	1	0.78	4.67	2.82	4.21	+	-	-	-	N
24	47446	SHRIN	37	2	4	30	-	10	Menorrhagia	2	1.34	4.82	4.51	5.06	+	-	-	-	N
25	43098	SUNANDA	43	3	12	18-20	-	45	Polymenorrhagia	6	1.52	8.90	1.86	0.91	+	-	-	-	N

26	39448	ROOPA	41	2	3	15	-	6	Polymenorrhoea	5	1.90	9.82	0.91	1.32	+	-	-	-	N
27	44369	PRABHAVATI	15	UN	2	28-30	+	10	Menorrhagia	2	0.76	4.19	2.58	2.81	+	-	-	-	N
28	40343	SAVITA	45	2	6	20	-	10	Polymenorrhagia	6	0.58	5.23	0.99	3.43	+	-	-	-	N
29	43232	SHANTALA	35	1	4	30	-	30	Menorrhagia	2	0.83	4.70	9.14	7.20	-	-	+	-	N
30	39997	MALLAMMA	40	0	12	20	-	8	Polymenorrhoea	5	0.85	8.23	4.60	4.16	+	-	-	-	N
31	44309	NANDANA	41	2	12	30-32	-	15	Menorrhagia	2	1.12	11.23	1.27	5.05	+	-	-	-	N
32	45085	PRIYANKA	34	1	18	60-80	+	20	Acyclical	1	0.89	10.54	1.08	0.91	+	-	-	-	N
33	43272	SULOCHANA	45	2	6	40	-	40	Oligomenorrhoea	4	0.97	5.48	3.18	2.08	+	-	-	-	N
34	45732	REKHA	19	UN	2	40-60	+	60	Oligomenorrhoea	4	3.05	13.43	0.29	1.98	-	-	-	+	N
35	43299	MANJULA	43	2	24	20-60	-	15	Acyclical	1	1.81	6.48	4.45	1.08	+	-	-	-	N
36	45154	SUVASHINI	39	3	18	30	+	5	Menorrhagia	2	1.13	8.13	0.71	3.43	+	-	-	-	N
37	43766	RAJASHREE	46	2	12	20-40	+	10	Metrorrhagia	3	1.47	7.40	0.81	4.13	+	-	-	-	N
38	39565	NAGAVENI	15	UN	2	15-20	+	12	Polymenorrhoea	5	0.87	4.88	3.92	0.98	+	-	-	-	N
39	46250	SHANTTHA	40	2	3	20	-	5	Polymenorrhagia	6	1.93	5.47	2.97	3.43	+	-	-	-	N
40	45110	KASTURABAI	22	UN	3	30	-	15	Menorrhagia	2	0.98	4.76	0.91	4.17	+	-	-	-	N
41	59173	JAYASREE	34	1	8	40	+	15	Menorrhagia	2	0.59	7.82	0.91	0.74	+	-	-	-	N
42	49243	SAVITA	41	2	12	45-60	-	10	Oligomenorrhoea	4	1.55	4.37	1.21	1.82	+	-	-	-	N
43	58880	SUVARNA	17	UN	2	35	+	4	Menorrhagia	2	0.98	4.07	7.14	9.12	-	-	+	-	N
44	46963	SHANAJ	40	4	6	40-60	-	18	Acyclical	1	1.34	11.13	5.12	2.42	+	-	-	-	N
45	43166	RAJASHREE	32	2	3	35	-	12	Menorrhagia	2	0.85	6.87	2.18	0.81	+	-	-	-	N
46	40808	NIRMALA	25	0	6	15	+	10	Polymenorrhoea	5	0.92	7.41	1.48	0.92	+	-	-	-	N
47	49207	RANI	43	1	6	36	-	30	Menorrhagia	2	1.45	4.87	0.97	1.17	+	-	-	-	N
48	47252	SHANTHA	18	UN	11	40	+	20	Oligomenorrhoea	4	0.63	4.80	1.08	1.82	+	-	-	-	N
49	43016	SHANKRAMMA	38	3	12	15-20	-	15	Polymenorrhagia	6	0.84	10.12	1.97	2.87	+	-	-	-	N
50	40725	VEERA	46	3	1	28	-	10	Menorrhagia	2	1.33	9.81	0.88	4.81	+	-	-	-	N
51	47115	SNEHALATA	45	3	14	20	+	12	Polymenorrhoea	5	1.51	6.85	3.81	3.84	+	-	-	-	N
52	47717	SUREKHA	31	1	26	30-90	+	10	Menorrhagia	2	1.67	7.43	4.12	4.81	+	-	-	-	N
53	47505	PRATIKSHA	16	UN	3	40	+	15	Menorrhagia	2	0.81	4.91	1.87	0.81	+	-	-	-	N
54	48177	BHARATHI	33	1	6	22	-	18	Polymenorrhagia	6	0.91	4.88	8.50	4.98	-	-	+	-	N
55	57968	GOURAMMA	43	2	7	15-30	-	20	Acyclical	1	1.59	10.03	0.99	0.44	+	-	-	-	N

56	47524	RACHITHA	21	0	4	45	+	25	Menorrhagia	2	1.19	11.50	2.81	1.21	+	-	-	-	N
57	39956	JUDHA	43	3	26	15	-	10	Polymenorrhagia	6	0.97	9.12	0.89	2.83	+	-	-	-	N
58	47389	SAVITRI	36	3	12	35	-	5	Menorrhagia	2	0.56	2.58	15.18	3.74	-	+	-	-	N
59	57701	SHAMSHAD	44	3	8	20	-	10	Polymenorrhagia	6	0.86	7.42	1.15	4.86	+	-	-	-	N
60	46250	SHANTHA	37	3	16	30	+	20	Menorrhagia	2	0.71	8.13	2.81	2.81	+	-	-	-	N
61	55176	SAKSHI	15	5	24	20	-	1	Polymenorrhagia	6	1.21	6.42	3.18	1.16	+	-	-	-	N
62	45110	KASTURABAI	45	UN	4	40-50	-	35	Menorrhagia	2	1.05	5.16	3.59	1.87	+	-	-	-	N
63	45428	NEELA	47	3	3	20	+	10	Polymenorrhagia	6	1.81	6.42	4.05	1.88	+	-	-	-	N
64	39565	NAGAVENI	39	2	6	30	+	15	Menorrhagia	2	0.91	8.23	0.97	2.08	+	-	-	-	N
65	55166	FARIDA	42	3	24	15	-	10	Polymenorrhoea	5	0.74	8.41	1.82	1.66	+	-	-	-	N
66	45732	REKHA	28	0	12	35	-	15	Menorrhagia	2	0.98	7.42	2.13	3.09	+	-	-	-	N
67	40830	RENUKA	45	2	8	30	-	5	Menorrhagia	2	1.61	9.41	1.88	1.88	+	-	-	-	N
68	40834	PRAVATHI	44	2	6	30-90	-	20	Acyclical	1	0.83	10.12	0.81	2.47	+	-	-	-	N
69	45085	PRIYANKA	17	UN	4	30	+	4	Menorrhagia	2	0.41	6.24	2.45	3.43	+	-	-	-	N
70	45847	MALLAMMA	43	4	12	40-60	-	10	Oligomenorrhoea	4	1.27	5.41	0.88	1.81	+	-	-	-	N
71	46237	MANANDA	33	2	24	25-40	-	20	Acyclical	1	0.88	6.83	1.12	2.43	+	-	-	-	N
72	46739	JAYAKKA	43	3	8	30	+	5	Menorrhagia	2	1.56	8.12	1.43	2.81	+	-	-	-	N
73	46852	RAHANA	34	2	36	15	-	5	Polymenorrhoea	5	0.95	9.41	4.15	0.81	+	-	-	-	N
74	41583	SUNANDA	45	3	6	25	+	10	Menorrhagia	2	0.56	10.23	3.07	0.94	+	-	-	-	N
75	46700	CHAYA	15	UN	4	20	-	18	Oligomenorrhoea	4	2.81	13.05	0.15	2.81	-	-	-	+	N
76	40834	PARVATHI	34	1	16	30-40	-	20	Acyclical	1	1.19	11.04	1.01	1.82	+	-	-	-	N
77	46642	AMBIKA	46	2	12	40	-	8	Menorrhagia	2	0.88	6.83	0.99	0.82	+	-	-	-	N
78	40746	SHREYA	18	UN	12	15	+	4	Oligomenorrhoea	4	1.96	5.13	2.83	0.71	+	-	-	-	N
79	46508	JAYANTHI	37	1	4	30-40	-	20	Metrorrhagia	3	0.52	4.78	1.18	0.89	+	-	-	-	N
80	46456	ANJALI	25	UN	26	30	-	15	Menorrhagia	2	1.05	4.98	9.81	3.81	-	-	+	-	N
81	60816	LIMBAWWA	35	1	5	20-22	+	15	Polymenorrhagia	6	0.67	3.18	0.91	1.82	+	-	-	-	N
82	69689	LAXMIBAI	37	1	12	20-60		10	Acyclical	1	0.82	8.29	1.23	2.17	+	-	-	-	N
83	60415	SUREKHA	15	UN	1	30	+	20	Menorrhagia	2	0.69	4.90	10.18	8.14	-	-	+	-	N
84	70146	RAJAKKA	35	2	8	30-35	-	6	Menorrhagia	2	1.81	381	4.14	3.93	+	-	-	-	N
85	70296	VEERABAI	40	UN	24	40	-	5	Menorrhagia	2	0.73	6.63	3.04	0.5	+	-	-	-	N

86	2432	SUNANDA	22	0	12	60	+	15	Oligomenorrhoea	4	0.91	4.94	2.21	2.62	+	-	-	-	N
87	71934	ARIFA	40	2	10	20-25	-	10	Polymenorrhagia	6	0.95	7.68	1.87	0.82	+	-	-	-	N
88	20169	MEENAKSHI	18	UN	2	30-35	+	12	Menorrhagia	2	1.52	11.54	0.81	1.81	+	-	-	-	N
89	72567	GOURAMMA	45	7	12	15-20	-	10	Polymenorrhagia	6	0.91	8.96	1.72	2.78	+	-	-	-	N
90	60526	SAVITRI	38	2	14	30-90	-	18	Acyclical	1	0.78	10.57	2.83	0.41	+	-	-	-	N
91	78138	SREDEVI	40	2	18	30	+	30	Menorrhagia	2	0.87	11.50	4.50	3.18	+	-	-	-	N
92	73799	RAGINI	17	UN	4	15	+	15	Oligomenorrhoea	4	0.58	4.58	3.43	1.26	+	-	-	-	N
93	82996	KALAMMA	43	3	6	15-20	-	10	Polymenorrhagia	6	1.45	8.19	2.48	4.81	+	-	-	-	N
94	54888	JAYA	37	2	3	40	-	4	Menorrhagia	2	0.82	4.91	11.81	4.87	-	-	+	-	N
95	73905	BHARATI	41	3	2	30-35	-	15	Menorrhagia	2	0.68	5.10	0.98	1.82	+	-	-	-	N
96	76696	MEERA	15	UN	1	30	+	10	Menorrhagia	2	0.75	8.18	3.41	3.44	+	-	-	-	N
97	60723	SANGAMMA	39	2	8	20	-	45	Oligomenorrhoea	4	0.84	8.81	2.48	4.62	+	-	-	-	N
98	76352	SUJATA	24	0	16	30	+	30	Menorrhagia	2	0.75	4.98	1.82	1.92	+	-	-	-	N
99	88497	GURUDEVI	44	2	24	20	+	5	Polymenorrhagia	6	0.55	10.18	2.81	0..87	+	-	-	-	N
100	61311	SHANTHA	18	0	6	15-30	+	15	Acyclical	1	0.92	8.12	4.50	1.62	+	-	-	-	N
101	89281	VIMALA	32	1	12	30	-	10	Menorrhagia	2	0.71	3.81	19.87	9.11	-	+	-	-	N
102	76043	GOURAWWA	35	2	18	26-30	-	5	Menorrhagia	2	0.75	8.47	1.23	0.81	+	-	-	-	N
103	91767	LAXMIBAI	42	2	6	20-24	-	15	Polymenorrhoea	5	0.91	11.12	2.47	2.08	+	-	-	-	N
104	62348	NALINI	19	UN	6	55-70	+	20	Oligomenorrhoea	4	0.89	4.68	1.82	3.43	+	-	-	-	N
105	88640	KALPANA	34	1	10	20-60	-	15	Acyclical	1	0.98	8.13	1.73	1.80	+	-	-	-	N
106	63833	SANGANNA	37	2	3	30	-	40	Menorrhagia	2	1.32	11.23	0.99	0.91	+	-	-	-	N
107	75922	SUJATHA	22	UN	12	30-35	+	10	Menorrhagia	2	1.9	8.91	1.08	0.58	+	-	-	-	N
108	101663	MANGALA	43	4	16	20-25	-	15	Polymenorrhagia	6	0.83	5.83	2.97	1.27	+	-	-	-	N
109	63397	NANDINI	17	UN	4	70-75	+	10	Metrorrhagia	3	0.65	7.41	3.08	2.78	+	-	-	-	N
110	102571	SAHEEN	41	5	24	30-50	-	12	Acyclical	1	0.69	8.13	4.91	1.29	+	-	-	-	N
111	72500	PUSHPA	34	1	1	15	-	10	Polymenorrhoea	5	1.32	8.43	1.82	3.48	+	-	-	-	N
112	107423	SAVITA	44	2	3	30	-	35	Menorrhagia	2	0.71	4.81	9.12	7.16	-	-	+	-	N
113	99308	GEETA	29	0	6	35	+	5	Menorrhagia	2	0.89	8.14	2.82	0.81	+	-	-	-	N
114	72053	BOURAMMA	34	2	4	20	-	10	Polymenorrhagia	6	0.71	9.08	1.67	1.23	+	-	-	-	N
115	19121	LAXMI	20	1	36	32	-	18	Menorrhagia	2	0.68	10.12	0.97	0.78	+	-	-	-	N

116	24103	VIDYA	24	0	12	30	+	18	Menorrhagia	2	1.49	8.13	3.14	1.82	+	-	-	-	N
117	124454	MADHU	31	0	8	60	-	25	Acyclical	1	0.81	7.81	1.47	3.07	+	-	-	-	N
118	346203	BIJI	20	UN	6	40	-	10	Menorrhagia	2	1.56	8.12	3.95	0.91	+	-	-	-	N
119	119860	SIDDAMMA	35	2	18	20	+	18	Polyenorrhoea	5	1.72	9.83	0.98	2.87	+	-	-	-	N
120	115994	SHOBHA	42	3	12	42	-	5	Menorrhagia	2	0.77	10.43	1.82	1.08	+	-	-	-	N
121	111908	SULOCHANA	38	2	24	40	-	10	Oligomenorrhoea	4	0.85	11.12	2.87	3.78	+	-	-	-	N
122	346055	BHARATHI	36	3	8	25-60	+	15	Metrorrhagia	3	0.71	8.18	1.18	1.87	+	-	-	-	N
123	28139	SHANTAMMA	48	2	6	15	-	18	Polymenorrhagia	6	0.82	11.57	0.97	0.98	+	-	-	-	N
124	28450	CHETANA	18	0	4	25-60	-	20	Acyclical	1	1.54	4.98	2.83	4.68	+	-	-	-	N
125	27208	RATNABAI	45	3	12	15	-	5	Polymenorrhagia	6	1.38	8.12	1.48	3.23	+	-	-	-	N
126	119860	KAVITHA	31	1	4	35	+	10	Menorrhagia	2	0.91	4.89	9.25	8.91	-	-	+	-	N
127	365894	SUNANDA	22	0	3	40	-	25	Menorrhagia	2	1.98	2.58	11.50	61.18	-	+	-	-	N
128	100965	SANGAMMA	40	2	12	15-20	-	6	Polymenorrhagia	6	0.88	8.12	1.84	4.81	+	-	-	-	N
129	98810	INDIRA	39	3	18	25	-	20	Menorrhagia	2	0.98	11.14	2.84	3.23	+	-	-	-	N
130	99943	LALITHA	29	2	4	20	+	5	Polymenorrhagia	6	1.56	10.12	0.71	0.78	+	-	-	-	N
131	28441	MAHADEVI	45	3	3	30	-	10	Menorrhagia	2	0.91	11.57	1.87	2.62	+	-	-	-	N
132	16321	BHARATHI	34	UN	6	60	-	35	Oligomenorrhoea	4	0.83	8.17	0.43	3.17	+	-	-	-	N
133	101803	SUMA	35	3	12	28	-	8	Menorrhagia	2	1.20	5.08	1.83	1.08	+	-	-	-	N
134	101203	MAHESHWARI	36	2	3	45-60	+	10	Acyclical	1	1.53	5.17	3.71	0.97	+	-	-	-	N
135	101663	MANGALA	40	3	4	40	-	12	Menorrhagia	2	0.71	10.14	0.98	4.18	+	-	-	-	N
136	115994	SHOBHA	44	2	6	20	-	5	Polymenorrhagia	6	1.81	11.60	1.08	5.12	+	-	-	-	N
137	30425	ROOPA	23	0	6	20	-	10	Menorrhagia	2	0.81	3.98	8.18	4.12	-	-	+	-	N
138	97050	SAROJA	43	4	12	60	+	15	Acyclical	1	0.85	10.58	2.71	2.18	+	-	-	-	N
139	10321	SHANKRAMMA	35	2	12	25	+	18	Menorrhagia	2	1.35	11.47	3.81	1.38	+	-	-	-	N
140	93400	MAMTHA	33	1	6	15	+	5	Menorrhagia	2	0.71	10.82	4.08	1.04	+	-	-	-	N