PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN REPRODUCTIVE AGE GROUP WOMEN WITH ABNORMAL UTERINE BLEEDING

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CERTIFICATE

This is to certify that the dissertation titled “PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN REPRODUCTIVE AGE GROUP WOMEN WITH ABNORMAL UTERINE BLEEDING ” is the bonafide work done by Dr.V.HEMA between September 2008 to August 2009 during her M.D.,O.G., course at ISO - KGH, MMC Chennai.

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# CONTENTS

| S.No. | Title                      | Page No. |
|-------|----------------------------|----------|
| 1.    | INTRODUCTION               | 1        |
| 2.    | REVIEW OF LITERATURE       | 16       |
| 3.    | AIMS AND OBJECTIVES        | 24       |
| 4.    | MATERIALS AND METHODS      | 25       |
| 5.    | RESULTS AND ANALYSIS       | 30       |
| 6.    | DISCUSSION                 | 52       |
| 7.    | SUMMARY                    | 59       |
| 8.    | CONCLUSION                 | 62       |
| 9.    | BIBLIOGRAPHY               | 63       |
| 10.   | ABBREVIATION               |          |
| 11.   | PROFORMA                   |          |
| 12.   | MASTER CHART               |          |
INTRODUCTION

Abnormal uterine bleeding is aberrant menstruation characterised by changes in cycle length or duration of flow or both. AUB accounts for 10% of the gynaecology related complaints. Thyroid dysfunction is marked by large number of menstrual aberrations.

Both hypothyroidism as well as hyperthyroidism is associated with a variety of changes in reproductive function including delayed onset of puberty, anovulatory cycles and abnormally high foetal wastage.

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 elucidated. Moreover majority of the cases has subclinical hypothyroidism and easily pass unrecognized and is now increasingly recognised as a risk factor for menstrual problems, cardiovascular diseases and abnormal mental development in foetus. Danese MD et al recommend hypothyroidism is frequent enough to warrant consideration in women with menstrual dysfunction.

Hence this study is to evaluate the thyroid function in patients having abnormal menstrual bleeding in reproductive age groups which will be justifiable and will help in
A brief outline of the physiology of menstruation and thyroid function is essential for the better understanding of the causal relation.

**MENSTRUAL CYCLE PHYSIOLOGY**

The normal menstrual cycle represents a complex interrelationship of hormones and physiological events in the hypothalamus, the pituitary, the ovary, and the uterus that prepares the body for the possibility of conception. An understanding of these relationships is essential for evaluation of menstrual irregularities.

**NORMAL MENSTRUAL CYCLE**

- Defined as having a mean interval of 21-35 days, with duration of 2 -7 days, menstrual flow of approximately 30ml per cycle, with an upper limit of normal at 60-80 ml.

For normal cycles to occur, the following conditions must be present,

- Intact Hypothalamic–pituitary system
- Normal ovary with normal follicular components
- Normal endometrium, capable of responding to ovarian steroids
- Intact thyroid and adrenal functions.

Thyroid and adrenal functions has to be intact, because their aberrations exert a deleterious effect on the hypothalamic–pituitary–gonadotrophin system.

**SEGMENTS:**

The normal human menstrual cycle can be divided into two segments.
The ovarian cycle consists of Follicular phase and Luteal phase. The uterine cycle is divided into Proliferative phase and Secretory phase.

**FOLLICULAR PHASE:**

This phase begins with sloughing of endometrium in day one of cycle and culminates with ovulation. It lasts for approximately 14 days. Estrogen is the predominant hormone of the follicular phase. Hormonal feedback promotes orderly development of a single dominant follicle, which should be mature at midcycle and prepared for ovulation.

**LUTEAL PHASE:**

The luteal phase is also called the secretory phase. An important role is played by the corpus luteum, the solid body formed in an ovary after the egg has been released from the ovary into the fallopian tube. This body continues to grow for some time after ovulation and produces significant amounts of hormones, particularly progesterone.

Progesterone plays a vital role in making the endometrium receptive to implantation of the blastocyst and supportive of the early pregnancy; it also has the side effect of raising the basal body temperature.

After ovulation, the pituitary hormones FSH and LH cause the remaining parts of the dominant follicle to transform into the corpus luteum, which produces progesterone.
and estrogens. The hormones produced by the corpus luteum also suppress production of the FSH and LH that the corpus luteum needs to maintain itself. Consequently, the level of FSH and LH fall quickly over time, and the corpus luteum subsequently atrophies. Falling levels of progesterone trigger menstruation and the beginning of the next cycle. From the time of ovulation until progesterone withdrawal has caused menstruation to begin, the process typically takes about two weeks, with ten to sixteen days considered normal.

**MENSES:**

Absence of conception & cessation of glandular secretion

↓

Irregular breakdown of endometrium

↓

Shedding of Decidua functionalis

↓

Menses

The destruction of the corpus luteum and its production of estrogen and progesterone is the cause of the shedding.
ABNORMAL MENSES - TERMINOLOGY

RELATIONSHIP BETWEEN ENDOMETRIAL, ENDOCRINE AND OVARIAN CYCLE
THE THYROID GLAND
A brief description of Thyroid physiology and its effect on menstruation is discussed here. The Thyroid (meaning “a shield”, because it shields the trachea) was first described by Wharton in the 19th century, weighs around 20 gms in the adult. The thyroid begins to function in the mid trimester of fetal life.

Microscopically, the gland contains 3 million follicles containing colloid which is made up of thyroglobulin.

CHEMISTRY
The Thyroid gland secretes three hormones, Thyroxine (T4), Triiodothyronine (T3) and Calcitonin. In normal adult about one third of T4 secreted per day is converted into T3 in the liver and kidney. About 80% of T3 generated outside the gland. T3 is 3-5 times more potent than T4. T3 is responsible for most of the thyroid action.

RECEPTORS
The nuclear receptors for thyroid hormones are of two types α and β. These receptors are ubiquitous and this explains its wider action in the body. T3 is more effective because of greater affinity (10 fold) for thyroid receptors.
ACTION OF THYROID HORMONES ON REPRODUCTIVE SYSTEM

Thyroid hormones have pronounced effects on the growth and development, metabolism and on every body system.

The following facts explain the role of thyroid on reproductive physiology

- TSH receptors are found on granulosa cells.
- T3 and T4 have been found in follicular fluids
- T4 has been found to enhance the action of gonadotrophins in
luteinisation and progesterone secretion.

The female hormonal milieu and its potential effects on immune surveillance play a role in the increased risk of women to develop autoimmune thyroid disease. The immunoglobulins produced against the thyroid are polygonal and the multiple combinations of various antibodies present combine to create the clinical spectrum of autoimmune thyroid diseases that affect successful reproductive function.  

**HYPOTHYROIDISM**

Hypothyroidism is one of the most common disorders encountered in endocrinological office practice. Thyroid disorders are 10 times more common in women than men (Morgante et al 1999).

The prevalence of overt hypothyroidism varies among different surveys from 0.1% to 2%. Subclinical hypothyroidism is much more prevalent and can be seen in as many as 15% of older women.

It results from reduced thyroid hormone actions at the peripheral tissues. This reduction in thyroid hormone action is in the vast majority of cases secondary to reduced thyroid hormone synthesis and secretion by the thyroid gland. Occasionally, peripheral resistance to thyroid hormone is the culprit.

Potential causes for hypothyroidism

- Primary
- Congenital absence of the thyroid gland
- External thyroid gland radiation
- Familial disorders of thyroxine synthesis
- Hashimotto thyroiditis
- Iodine-131 ablation for Grave’s disease
- Ingestion of Antithyroid drugs
- Iodine deficiency
- Idiopathic myxoedema
- Surgical removal of Thyroid gland

➢ Secondary

- Hypothalamic TRH deficiency
- Pituitary or Hypothalamic tumours or disease.

**Primary hypothyroidism**

Primary hypothyroidism is responsible for the majority of hypothyroid cases. The following discussion reviews the most common entities that result in primary hypothyroidism.

- Chronic autoimmune thyroiditis is the leading cause of primary hypothyroidism in iodine deficient areas. Clinically patients with Hashimotto’s thyroiditis may present with or without goitre. Pathophysiologically, there is cell mediated and antibody mediated
destruction of the Thyroid gland.

- Iodine deficiency causes Hypothyroidism. Patients often have large goitres.
- Post ablative hypothyroidism develops several weeks after radioactive iodine therapy.

Secondary hypothyroidism

In secondary hypothyroidism the defect is in the pituitary or in the hypothalamus. From a practical point of view, the end result is the same: a reduction in biologically active TSH. In clinical practice, pituitary adenomas are the most common cause of central hypothyroidism. Depending on the damage incurred by the hypothalamus-pituitary axis, central hypothyroidism may be reversible or permanent.

EFFECT OF HYPOTHYROIDISM IN ADULT WOMEN

Severe hypothyroidism is associated with diminished libido, oligomenorrhea, amenorrhea, or anovulation. Secretion of progesterone is inadequate and endometrial proliferation persists resulting in excessive and irregular breakthrough bleeding. Hypothyroidism appears to be associated with decreased fertility resulting from ovulatory difficulties and spontaneous abortions may result.

The values of plasma gonadotrophins are usually in the normal range in primary hypothyroidism. In postmenopausal women, the levels are usually lower than euthyroid women of the same age but are nevertheless within the menopausal range. This provides a valuable means of differentiating primary from secondary hypothyroidism.
Myxedematous infiltration can produce enlarged, cystic ovaries.

**METABOLISM OF OESTROGENS IN HYPOTHYROIDISM**

The metabolism of estrogens is altered with respect to oestradiol and estrone, hypothyroidism favours the metabolism of steroids via 16 alpha hydroxylation over that via 2- oxygenation with the result the formation of oestriol is increased and that of 2-hydroxyestrone and its derivative 2-methoxyestrone is decreased. The sex hormone binding globulin concentrations in plasma is decreased with the result the plasma concentrations of both testosterone and oestradiol are decreased, but the unbound fractions are increased. Fortunately, the alterations in steroid metabolism are corrected by restoration of the euthyroid state.

**HYPERPROLACTINEMIA IN HYPOTHYROIDISM**

Patients with primary hypothyroidism may have mild to moderate serum prolactin elevation due to increased prolactin secretion under the stimulatory effect of TRH. A decrease in T3 feedback in hypothyroidism may induce an increase in the hypothalamic TRH production. Hyperprolactinemia can result in hypogonadotropic hypogonadism. Hence there is reduced fertility and increased risk of miscarriage.

The duration of hypothyroidism is important with regard to the mechanism of amenorrhea, the longer the duration the higher the incidence of amenorrhea and higher the prolactin levels. This may be associated with decreasing hypothalamic content of dopamine with ongoing hypothyroidism. This would lead to an unopposed TRH stimulatory effect on the pituitary cells that secrete prolactin.
SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is the term used to define a state in which serum T3 and T4 levels are within normal limits, but there is underlying mild thyroid failure, as evidenced by a mild increase in serum TSH. The condition is sometimes designated as compensated, early, latent, mild, minimally symptomatic and preclinical hypothyroidism.

The aetiology of subclinical hypothyroidism is similar to that of overt hypothyroidism. Chronic autoimmune thyroiditis is the leading cause. Other common causes of subclinical hypothyroidism include thyroid ablation with radioactive iodine, partial thyroidectomy, antithyroid drugs, external beam irradiation, drugs such as amiodarone, lithium or radiographic contrast agents and inadequate T4 therapy for overt hypothyroidism.

Subclinical hypothyroidism represents the early stage of the disease, and it has been shown that there is progression to overt hypothyroidism in approximately 4% to 18% of patients who have subclinical hypothyroidism every year. The likelihood of progression to overt hypothyroidism increases in the presence of antithyroid antibodies, serum TSH values greater than 10µU/mL, positive history of radioiodine ablation therapy, history of external radiation therapy for nonthyroid malignancies, and chronic lithium treatment. At this time there is evidence that subclinical hypothyroidism is associated with hypertension, cardiac dysfunction and dyslipidemias. But importantly, women with subclinical hypothyroidism present with menstrual irregularities such as
menorrhagia or fertility problems.

**LABORATORY EVALUATION**

The diagnosis of hypothyroidism is based on the combination of clinical context and laboratory tests.

A number of factors affect the levels of TSH, total T4 and total T3. But the serum levels of free T4 remain normal in these circumstances and provide a better assessment of thyroid function. Patients who have primary hypothyroidism have elevated TSH and low FT4 and FT3. TPO antibodies are found in many patients who have hashimoto’s thyroiditis.

A repeatedly elevated TSH, between 4 and 15 mIU/mL, with normal FT4 and FT3 is suggestive of subclinical hypothyroidism 17.

| FREET3  | FREET4  | TSH   | DIAGNOSIS                  |
|---------|---------|-------|----------------------------|
| normal  | normal  | normal| Euthyroid status           |
| elevated| elevated| low   | Hyperthyroidism            |
| Low     | Low     | elevate| Hypothyroidism            |
|         |         | d     |                            |
| normal  | normal  | elevate| Subclinical hypothyroidism |
|         |         | d     |                            |
| normal  | normal  | low   | Subclinical hyperthyroidism|
REVIEW OF LITERATURE

In women with menstrual irregularities, Thyroid dysfunction has a major share in the aetiology. On the contrary, menstrual disturbances may be the first indication of underlying thyroid disorder.

- As early as in 1927, Gardner and Hill, showed an association between hypothyroidism and menorrhagia 18.

- Goldsmith et al in 1952 found that 8 out of 10 patients with hypothyroidism had ovulatory failure and only 2 had normal ovulation and menses 19.

- Rogers et al in 1958 found that, change in character of uterine bleeding and length of the cycle were the most common problems observed in hypothyroid women 20.

- Blum and Blum in 1972 studied the relationship between subclinical hypothyroidism and menorrhagia 21.

- Akande in 1975 stated that changes in FSH/LH ratios in hypothyroidism caused anovulatory cycles 22.

- Yuen B, keye, Knopff in 1976 demonstrated hyperprolactinemia causing luteal phase defect is associated with less severe forms of hypothyroidism 23.

- Andrew weeks et al in 1987 stated after analysing 650 women with menstrual irregularities that hypothyroidism is a greatly under diagnosed etiology for menorrhagia 24.

- Robuschi et al in 1987 have concluded in their study that hypothyroidism...
increases with age and is more common in older women. Up to 45% of thyroid tissue from women over 60 showed evidence of thyroiditis. The incidence of anti-thyroglobulin antibodies is 7.4% of women over age 75 while 16.9% of women aged 60 and 17.4% of women over age 75 had elevated TSH levels. In women admitted in Geriatric wards 2-4% had hypothyroidism.\textsuperscript{25}

- Klee et al 1987, are of opinion that TSH based testing strategies minimise the problem of abnormal T4 study and significantly reduce the number of TRH stimulation tests performed.\textsuperscript{26}

- Smith et al in 1987 found an association between hypothyroidism and menorrhagia with development of an advanced form of Von willebrand’s disease in untreated hypothyroidism. The haemostatic defects returned to normal with thyroxine replacement.\textsuperscript{27}

- Hingham in 1992 reported a case of hypothyroidism in which the menstrual loss was measured. An initial loss of 480 ml decreased to 58 ml following 3 months of treatment with thyroxine.\textsuperscript{28}

- Wilansky DL, Griesman B in 1992 performed Thyrotrophin releasing hormone (TRH) test in 67 women who complained of excessive menstrual loss. All had normal levels of thyroxine and thyrotrophin. They found that 22% had abnormal TRH tests and they treated these women with thyroxine. At follow up between 12 and 36 months later all considered their menstrual loss to be normal. In the 16 women with normal TRH tests, 56% still complained of menorrhagia.\textsuperscript{29}
• Blum and Blum in 1992 studied the possible relationship between menorrhagia and occult hypothyroidism in IUD wearing women. They studied 40 women with menorrhagia secondary to an intrauterine contraceptive device. They all had a normal free thyroxine and TSH levels. The 10 patients who had the highest TSH levels were given a TRH test and all proved to have early hypothyroidism. All patients reported a significant improvement with thyroxin treatment. 

• Joshi JV et al, 1993 in their study on 178 women referred to thyroid clinic found that, reproductive failure (infertility, pregnancy wastage, lactation failure) occurred in 37.5% of hypothyroid women against 16.3% of euthyroid and 16.7 % of healthy controls. Interestingly, in 45% of cases menstrual abnormality was antecedent to other clinical features by a variable period of two months to ten years. Reproductive dysfunction and lactation failure also preceded thyroid dysfunction or goitre.

• Danase MD et al in 1996 had stated that Hypothyroidism was frequent enough to warrant consideration in most elder women. They recommended screening with highly sensitive TSH assay every two years beginning at age 60 or with the appearance of any symptom suggesting hypothyroidism.

• Chameron & Fraser in 1998 in their article on the clinical disorders of the endometrium and the menstrual cycle had stated that thyroid disorders are the most common endocrine abnormality associated with menstrual disturbances. Hypothyroidism is a potent cause of menorrhagia amenable to treatment.
• Shaw RW in 1999 conducted a study to analyse the effect of thyroxine replacement on menstrual blood loss in hypothyroid patients. There was a relative improvement in haemoglobin concentration and general condition of the patients.

• Prentice et al – Medical management of menorrhagia – 1999 have stated that all women with unexplained menorrhagia should be tested for hypothyroidism.

• Krassas GE et al 1999- Disturbances of menstruation in hypothyroidism had stated that oligo-amenorrhea or hypermenorrhea-menorrhagia can be present in women having thyroid failure.

SUBCLINICAL HYPOTHYROIDISM

Huber G, Mitrache C, Gugliemetti M et al. Predictors of overt hypothyroidism and natural course: a long –term follow up study in impending thyroid failure-1998. In this follow up study of 450 patients of subclinical thyroid disease they found that the progression to overt hypothyroidism is approximately 4% to 18% every year. On further analysis they formulated the predictors which in a given patient increases the likelihood of progression to overt hypothyroidism. The predictors are

- TSH Levels >10 mIU/L
- symptoms and signs of thyroid failure
- convincing family history of thyroid disease
- Pregnant patients
- Strong habit of tobacco use
- Severe hyperlipidemia

Surks MI, Ortiz E, Daniels GH, et al. 2004, did a scientific review for formulating guidelines in management of subclinical thyroid disease. They concluded that subclinical thyroid disease is associated with significant clinical impairment in affected patients and if so treatment with levothyroxine gives better outcomes. The consensus was that there was good evidence that treatment of patients who have TSH levels above 4.5 mU/L prevents progression to overt hypothyroidism. And the evidence was convincing that early treatment was beneficial.  

Surks MI. 2005, proposed a joint statement on the screening of subclinical thyroid disease. Thyroid screening is recommended in high risk women, such as those who have a personal history of thyroid or other autoimmune disorders, or those who have a family history of thyroid disorders, or presenting with symptoms of thyroid failure.  

Universal screening of women for subclinical hypothyroidism and hypothyroixinemia is not recommended because there is no evidence to justify the efficacy of screening and treatment and there have been no interventional studies to prove that this improves outcome.  

Wilson GR, Curry RW Jr. Subclinical thyroid disease. 2005. They defined subclinical thyroid disease as a state in which serum T4 and T3 are within normal limits but there is mild increase in TSH. They are of opinion that patients with subclinical disease may be asymptomatic or may present with vague, non specific symptoms like
fatigue, generalised weakness, depression and memory, cognitive and sleep disturbances. As in other thyroid disease, there is female preponderance. Women with sub clinical thyroid disease may present with menstrual irregularities such as menorrhagia or fertility problems.

Wartofsky L et al - overt and subclinical hypothyroidism in women. They stated that mild thyroid failure represents early stage of the thyroid disease. Chronic autoimmune thyroiditis is the leading cause. Few other causes include

- Thyroid ablation with radioiodine
- Partial thyroidectomy
- Antithyroid drugs
- External beam radiation
- Drugs such as amiodarone and lithium
- Radiographic contrast agents.

Because of the increasing trend of autoimmune diseases, drug intake and radiation exposure the prevalence of thyroid diseases is on the rise.

Jorde Rolf et al, 2006 in a study on effect of treatment on subclinical thyroid disease reported that thyroxine replacement should become the standard care for patients who have subclinical thyroid disease. Future studies should shed more light on this subject.
AIM AND OBJECTIVES

This study aimed at analysing the cross sectional population,

➢ To determine the association between menstrual irregularities and thyroid function

➢ To analyse the pattern of menstrual dysfunction among women with thyroid disorder

➢ To estimate the prevalence of subclinical thyroid disease among reproductive age group women with abnormal uterine bleeding

➢ To analyse the possible predictors which in a given patient helps in early testing of thyroid function to diagnose them in the subclinical stage.
MATERIALS AND METHODS

STUDY DESIGN: Analytical study

STUDY PERIOD

August 2008 to September 2009

SAMPLE POPULATION:

The study population consisted of 250 women attending the gynaecology outpatient clinic, Institute of social obstetrics & Govt. Kasturba Gandhi hospital, with the following complaints in the age group of 18 to 45 years,

1. Oligomenorrhea – where the cycle length lasts longer than 35 days
2. Hypomenorrhea – lesser bleeding which lasts for 2 days or less.
3. Menorrhagia - cyclical bleeding at normal intervals which is excessive in amount (>60 ml/changes 6 pads per day/associated with clots)
4. Polymenorrhea - cyclical bleeding which is normal in amount, but occurs in intervals of <21 days.
5. Amenorrhea – absence of menstruation

The patients were selected on the basis of Inclusion and Exclusion criteria as follows:

Inclusion criteria:

- age group 18 to 45 years
- with any of menstrual disturbances described above
- no demonstrable pelvic pathology
- not an IUCD user
- not on thyroxine replacement therapy
- with symptoms of thyroid dysfunction.

**Symptoms of hyperthyroidism**

- ✓ Weight loss ( >10 kg in 3 months or subjective weight loss)
- ✓ Diarrhoea
- ✓ Heat intolerance
- ✓ Tremors
- ✓ Eye changes
- ✓ Palpitations

**Symptoms of hypothyroidism**

- ✓ Change of voice
- ✓ Weight gain
- ✓ Constipation
- ✓ Dryness of skin
- ✓ Cold intolerance
- ✓ Fatigue/lethargy
- ✓ Sleep disturbances

**Exclusion criteria**

- ➢ Women not in age group <18 and >45.
- ➢ Presence of palpable pelvic pathology
- ➢ With overt hypothyroidism on thyroxine.
- ➢ known thyroid disorders
On drugs like aspirin, heparin, antithyroid agents, steroids, amiodarone and lithium

After proper selection of patients a detailed menstrual history elicited and other details as per proforma enclosed.

A thorough history as to the presence of symptoms of hypothyroidism or hyperthyroidism was taken.

- Evaluation of general condition of patient (height, weight, BMI, anaemia, goitre, galactorrhoea)
- The cardiovascular, respiratory and nervous systems were evaluated
- Gentle abdominal, speculum and internal examination done
- 5 ml of venous blood was taken in a plain glass tube without any anticoagulant: morning sample in a fasting state taken and serum was separated to estimate free T3, T4 & TSH.
- FreeT3 & Free T4 assay was done using competitive EIA and TSH by sandwich enzyme linked immunosorbent assay using kit supplied by Lilac Medicare pvt. Limited, Mumbai.

• THYROID –REFERENCE RANGE
**HORMONE** | **REFERENCE RANGE**
---|---
TSH | 0.5 – 5.0 mIU/L
FREE T3 | 1.7 – 4.2 pg/ml
FREET4 | 0.30 – 5.5 µIU/Ml

- **BMI** was calculated by the formula

\[
\text{Body mass index} = \frac{\text{weight in kg}}{\text{height in m}^2}
\]

**Standards**

| BMI   | Inference        |
|-------|------------------|
| <18   | Lean             |
| 18 - 24 | Normal         |
| 25 - 29 | Overweight   |
| 30 - 34 | Obese         |
| >35   | Morbid obesity  |
### RESULTS & ANALYSIS

#### TABLE 1

**AGE DISTRIBUTION IN STUDY GROUP**

| AGE GROUP    | FREQUENCY | PERCENTAGE |
|--------------|-----------|------------|
| 18-24 years  | 36        | 14.4%      |
| 25-31 years  | 103       | 41.2%      |
| 32-39 years  | 81        | 32.4%      |
| >40 years    | 30        | 12.0%      |

Among the 250 women under study majority were in the age group 25-31 years (41.2%).
TABLE 2

Distribution of cases according to PARITY

| PARITY    | FREQUENCY | PERCENTAGE |
|-----------|-----------|------------|
| NULLIPARA | 27        | 10.8%      |
| P1L1      | 62        | 24.2%      |
| P2L2      | 98        | 39%        |
| MULTIPARA | 63        | 25%        |

Majority of patients were P2L2.

![Parity Distribution of Study Group]

TABLE - 3

REPRODUCTIVE DYSFUNCTION IN STUDY GROUP

| REPRODUCTIVE DYSFUNCTION | NUMBER | PERCENTAGE |
|--------------------------|--------|------------|
| Nil                      | 214    | 85.6%      |
Among 250 women in reproductive age group with AUB presented to general gynaec clinic, 5.6% had infertility and 8.8% had history of abortions
| TYPE OF AUB     | FREQUENCY | PERCENTAGE |
|----------------|-----------|------------|
| Amenorrhea     | 25        | 10%        |
| Menorrhagia    | 148       | 59.2%      |
| Oligomenorrhea | 68        | 27.2%      |
| Hypomenorrhea  | 4         | 1.6%       |
| Polymenorrhea  | 5         | 2%         |

Majority in study group had menorrhagia (59.2%) and oligomenorrhea (27.2%).
Many patients in the sample presented with AUB of 4-6 months duration.

TABLE – 6

SYMPTOMS OF THYROID DYSFUNCTION

| SYMPTOMS     | NUMBER | PERCENTAGE |
|--------------|--------|------------|
| Asymptomatic | 181    | 72.4%      |
| Weight gain  | 20     | 8%         |
Symptoms of thyroid dysfunction

72.4% of patients had no symptoms of thyroid dysfunction. Weight gain (8%) was the most frequent symptom.
## SIGNS OF THYROID DYSFUNCTION

| SIGNS                        | NUMBER | PERCENTAGE |
|------------------------------|--------|------------|
| Slow movements              | 13     | 5.2%       |
| Coarse skin                 | 15     | 6%         |
| Cold skin                   | 14     | 5.6%       |
| Periorbital puffiness       | 6      | 2.4%       |
| Delayed ankle jerk          | 2      | 0.8%       |
| Myxoedema                   | 2      | 0.8%       |
| Bradycardia                 | 5      | 2.0%       |

![Bar chart showing the number and percentage of each sign of thyroid dysfunction]
### TABLE -7

**GENERAL EXAMINATION**

| General examination | Number | Percentage |
|---------------------|--------|------------|
| Normal              | 191    | 76.4%      |
| Anaemia             | 59     | 23.6%      |
| Goitre              | 0      |            |

23.6% of patients had clinical anaemia and the rest were normal.
### TABLE - 8

**BMI- BODY MASS INDEX**

| BMI RANGE             | NUMBER | PERCENTAGE |
|-----------------------|--------|------------|
| <18(lean)             | 3      | 1.2%       |
| 18-24(normal)         | 202    | 80.8%      |
| 25-29(overweight)     | 24     | 9.6%       |
| 30-34(obese)          | 16     | 6.4%       |
| >34(morbid obesity)   | 5      | 2.0%       |
TABLE - 9
GYNAECOLOGICAL EXAMINATION

| CLINICAL UTERINE SIZE | NUMBER | PERCENTAGE |
|-----------------------|--------|------------|
| Normal                | 242    | 96.8%      |
| Bulky uterus          | 8      | 3.2%       |

TABLE - 10
HAEMOGLOBIN ESTIMATION

| Haemoglobin in gms% | number | Percentage |
|---------------------|--------|------------|
| <11gms              | 59     | 24%        |
| >11gms              | 191    | 76.4%      |

TABLE – 11
DILATATION & CURETTAGE

| ENDO METRIAL HISTOLOGY | NUMBER | PERCENTAGE |
|------------------------|--------|------------|
| Secretory              | 55     | 22%        |
| Proliferative          | 177    | 70.8%      |
### Hyperplasia

| USG findings  | Number | Percentage |
|---------------|--------|------------|
| Normal        | 201    | 80.2%      |
| Bulky uterus  | 12     | 4.8%       |
| Cystic ovaries| 37     | 15%        |

**TABLE - 12**

ULTRASONOGRAM

| USG findings  | Number | Percentage |
|---------------|--------|------------|
| Normal        | 201    | 80.2%      |
| Bulky uterus  | 12     | 4.8%       |
| Cystic ovaries| 37     | 15%        |

**TABLE – 13**

T3 VALUES (1.7-4.2 pg/ml)

| T3 (pg/ml) | Number | PERCENTAGE |
|------------|--------|------------|
| < 1.7      | 39     | 15.6%      |
| 1.7-4.2    | 193    | 77.2%      |
| >4.2       | 18     | 7.2%       |

**TABLE - 14**

T4 VALUES (0.70-1.80 ng/ml)

| T4(ng/ml) | NUMBER | PERCENTAGE |
|-----------|--------|------------|
| <0.70     | 39     | 15.6%      |
| 0.70-1.80 | 193    | 77.2%      |
| >1.80     | 18     | 7.2%       |

**TABLE - 15**
TSH VALUES (0.5-5.0 mIU/ml)

| TSH  | NUMBER | PERCENTAGE |
|------|--------|------------|
| <5.0 | 18     | 7.2%       |
| 0.5-5.0 | 173   | 69.2%      |
| >5.0 | 59     | 23.6%      |
### TABLE - 16

**TYPE OF THYROID DYSFUNCTION**

| TYPE OF THYROID DYSFUNCTION | NUMBER | PERCENTAGE |
|----------------------------|--------|------------|
| HYPOTHYROIDISM              | 39     | 15.6%      |
| NORMAL                      | 173    | 69.2%      |
| HYPERTHYROIDISM             | 18     | 7.2%       |
| SUBCLINICAL HYPOTHYROIDISM  | 20     | 8.0%       |

**DISTRIBUTION OF THYROID DYSFUNCTION**
TABLE - 17

RELATION OF AGE WITH THYROID DYSFUNCTION

Cross table

According to the above data, there is significant association (p<0.001) between age and thyroid dysfunction. With increasing age, thyroid dysfunction increases.

AGE & THYROID DYSFUNCTION

![Bar chart showing the relation between age and thyroid dysfunction]
TABLE - 18
TYPE OF AUB AND THYROID DYSFUNCTION

TYPE OF AUB AND THYROID DYSFUNCTION

![Bar chart showing the distribution of Type of AUB and Thyroid Dysfunction](chart.png)
Among 39 women with hypothyroidism, 29(61.6%) had menorrhagia and 7(25.6%) had amenorrhea.
Oligomenorrhea (94.5%) was more frequent in hyperthyroid women.

Table - 21

MENSTRUAL DYSFUNCTION IN SUBCLINICAL HYPOTHYROIDISM

| Menstrual dysfunction | Subclinical hypothyroidism | Percentage |
|-----------------------|---------------------------|------------|
| Oligomenorrhea        | 2                         | 5%         |
| Menorrhagia           | 14                        | 70%        |
| Amenorrhea            | 4                         | 25%        |
| Hypo & polymenorrhea  | 0                         | 0          |

Among 20 women detected to have early hypothyroidism, 14(75%) had menorrhagia, 4(25%) had amenorrhea and 2(5%) had oligomenorrhea.

According to the above available data, there is a significant correlation (p<0.001) between type of menstrual dysfunction and thyroid dysfunction.
**Table – 22**

**DURATION Vs THYROID DYSFUNCTION**

| AUB DURATION | NORMAL | THYROID DYSFUNCTION | TOTAL |
|--------------|--------|---------------------|-------|
| 1-3 months   | 38     | 10                  | 48    |
| % of total   | 15.2%  | 4%                  | 19.2% |
| 4-6 months   | 95     | 30                  | 125   |
| % of total   | 38%    | 12%                 | 50%   |
| 7mon –1 yr   | 20     | 21                  | 41    |
| % of total   | 8.0%   | 8.4%                | 16.4% |
| 1-2 yrs      | 13     | 11                  | 24    |
| % of total   | 5.2%   | 4.4%                | 9.6%  |
| >2 years     | 2      | 3                   | 5     |
| % of total   | 0.8%   | 1.2%                | 2%    |
| Since menarche | 5    | 2                   | 7     |
| % of total   | 2%     | 0.8%                | 2.8%  |
| TOTAL        | 173    | 77                  | 250   |
| % of total   | 69.2%  | 30.8%               | 100%  |

**DURATION OF AUB & THYROID DYSFUNCTION**
According to the above data, there is significant correlation (p<0.05) between duration of menstrual symptoms and presence of thyroid dysfunction.

Table - 23
BMI AND HYPOTHYROIDISM

| BMI               | HYPOTHYROID WOMEN-NUMBER | PERCENTAGE |
|-------------------|---------------------------|------------|
| <18 (underweight) | 0                         | 0          |
| 18-24 (normal)    | 11                        | 28.3%      |
| 25-29 (overweight)| 13                        | 33.4%      |
| 30-34 (obese)     | 12                        | 30.7%      |
| >34 (morbid obesity) | 3                        | 7.6%       |

Women with abnormal BMI showed more occurrence of hypothyroidism.

Table – 24
## BMI & HYPERTHYROIDISM

| BMI   | HYPERTHYROID- NUMBER | PERCENTAGE |
|-------|----------------------|------------|
| <18   | 1                    | 33.3%      |
| 18-24 | 14                   | 69.3%      |
| 25-30 | 3                    | 12.5%      |
| 31-34 | 0                    | 0          |
| >34   | 0                    | 0          |
| BMI     | Normal | Presence of Thyroid dysfunction | Total |
|---------|--------|---------------------------------|-------|
| <18     | 2      | 1                               | 3     |
| % of total | 0.8%  | 0.4%                            | 1.2%  |
| 18-24   | 158    | 44                              | 202   |
| % of total | 63.2% | 17.6%                           | 80.8% |
| 25-29   | 8      | 16                              | 24    |
| % of total | 3.2%  | 6.4%                            | 9.6%  |
| 30-34   | 3      | 13                              | 16    |
| % of total | 1.2%  | 5.2%                            | 6.4%  |
| >34     | 2      | 3                               | 5     |
| % of total | 0.8%  | 1.2%                            | 2.0%  |
| Total   | 173    | 77                              | 250   |
|         | 69.2%  | 30.8%                           | 100%  |

According to the above data, women with abnormal BMI had abnormalities in thyroid function.
BMI<18
18-24
25-29
30-34
>34

Normal
Thyroid dysfunction
Table -26

REPRODUCTIVE DYSFUNCTION AND THYROID DISORDERS

| Reproductive Dysfunction | No Thyroid Dysfunction | Thyroid Disorders | Total |
|--------------------------|------------------------|------------------|-------|
| NIL                      | 156                    | 58               | 214   |
| % of total               | 62.4%                  | 23.2%            | 85.6% |
| Infertility              | 8                      | 6                | 14    |
| % of total               | 3.2%                   | 2.4%             | 5.6%  |
| Pregnancy Wastage        | 9                      | 13               | 22    |
| % of total               | 3.6%                   | 5.2%             | 8.8%  |
| Total                    | 173                    | 77               | 250   |
| % of total               | 69.2%                  | 30.8%            | 100%  |

Reproductive failure & Thyroid dysfunction
From the above data it is derived that there is significant correlation (p<0.05) between reproductive dysfunction and presence of thyroid disorders.
DISSCUSION

Abnormal uterine bleeding is a benign yet debilitating disease with a strong association with thyroid disorders. This study highlights the association between AUB and Thyroid dysfunction by measurement of free T3, free T4, and TSH.

• In our study, the mean age of women with thyroid dysfunction was 36 years. C A Petta et al 2007 in their cross sectional study carried out in 148 women with menstrual dysfunction found a mean age of 34.6 years.

Vanderpump MP et al 1995, in their 20 years follow up of whicham survey had a mean age of 34 years for occurrence of thyroid disorders. They also stated development of hypothyroidism increases with age but no age relation for hyperthyroidism. Sampath S et al 2007, in their study on clinicobiochemical spectrum of hypothyroidism found a mean age of 36.2 years among 944 women referred for thyroid testing. Also, they found that the mean age of females with subclinical hypothyroidism is 5.4 years less than those with overt hypothyroidism.

• In this study we found an association in the occurrence of menorrhagia (59.2%) in hypothyroid women. In a retrospective analysis by Andrew D Weeks 2000, among 50 patients with myxoedema, 28 (56%) had menstrual disturbances and the most common complaint was menorrhagia (36%). Col P Singh et al 2007, in their analysis of menstrual dysfunction among hypothyroid women stated, ‘menorrhagia was seen in 32.4% of hypothyroid women’.

• Also in the present study, oligomenorrhea (94.5%) was more frequent in women
found to have hyperthyroidism. This association correlated with the findings in other studies. Tunbridge et al -2002, in their study on analysis of bleeding pattern in hyperthyroid subjects, detected Oligomenorrhea to be more frequent in hyperthyroid subjects with the occurrence of 80% 46. In another study by Daniels -2004 had a 85% prevalence of Oligomenorrhea in hyperthyroid patients 47. Hence, screening of thyroid function in these women with menstrual dysfunction is of great significance.

- In community surveys, it has been detected that women developing milder or early forms of hypothyroidism may have menstrual abnormalities as the presenting feature48-50. In this study, women diagnosed of subclinical hypothyroidism presented with menorrhagia (75%) and amenorrhea (20%). On comparison with other studies, this association is significant. Wilson GR et al, in their article on subclinical thyroid disease, stated the menstrual dysfunction in preclinical hypothyroids will be similar to that in overt hypothyroidism39. The findings of the present study correlated with the 76% occurrence of Oligomenorrhea 16% occurrence of amenorrhea in a study by Jorde et al on endocrinological disturbances in hypothyroid women51.

- Another association found in the study was correlation of thyroid dysfunction with duration of menstrual dysfunction. Majority patients presented with abnormal bleeding of > 4 months duration had increased occurrence of thyroid abnormalities(85%). This correlation is found in a similar study by Sampath et al
on clinicobiochemical spectrum of thyroid disease, according to them, 65% of women had their onset of menstrual complaint before mean duration of 6 months.

• In the present study, among 39 women detected to have hypothyroid, 20 (51%) had weight gain as their complaint followed by fatigue in 7 (28%) women. Out of 18 patients with hyperthyroidism, weight loss (43%) and anxiety (23%) were the clinical symptoms. Complaints of almost all symptoms related with hypo/hyperthyroidism were statistically more frequent among women with thyroid dysfunction. The symptoms of thyroid dysfunction were more predictive of the disease. This has been previously demonstrated in other studies. Sampath S et al 2007, on their analysis on clinical presentation of hypothyroid cases found weight gain as the commonest symptom (53.8%) followed by generalized weakness (36%).

The most specific and discriminating feature of hypothyroidism are decreased sweating, hoarseness of voice, paresthesias, cold intolerance (Utiger RD et al 1995). However in this study, we found symptom of weight gain (51%) was more common.

• In the present study, hyperthyroid subjects, presented with symptom of weight loss (56%) and anxiety (39%). This frequency was similarly stated in other studies. Stoffer SS et al, clinical features of patients with Grave’s disease, detected that loss of weight (74%) and anxiety (53%) symptoms are the prominent features. Vitti P et al, in their analysis on clinical presentation of graves disease found heat intolerance and tremors were common. But in our study, we found
weight loss (56%) and anxiety (39%) to be common.

- BMI abnormality in the sample population of the present study correlated well with thyroid abnormalities. Women with normal BMI had less occurrence of thyroid dysfunction (19.3%) in contrast to those with high BMI who had 62.2% occurrence. This association is well proved in other studies. Tomlinson et al, in their analytical study on clinical and endocrinological characteristics of obese women cited a 65% incidence of thyroid dysfunction among women with abnormal BMI. Similar incidence of 72% was concluded by Pi-Sunyer FX et al in their analysis on medical hazards of obesity.

- In this study, the presence of infertility (2.4%) and h/o abortions (5.2%) were associated with significant thyroid abnormalities. Though significance is cited the prevalence is not in agreement with 29% prevalence of thyroid dysfunction described by Poppe et al 2002 in their study on thyroid dysfunction in infertile women and in another study by Sampath et al (2007), where 34.3% of infertile women and 10.2% of women with pregnancy wastage had thyroid failure. Because in the previous two studies, the sample population consisted of women with infertility and recurrent pregnancy loss. Whereas in the present study, the sample population was taken from the general gynaec clinic which would have accounted for the less prevalence.

In an analysis on prevalence of hypothyroidism in women referred for gynaec complaints by Ram Chandra rao et al- 2008, quoted a prevalence of 4.2% among...
infertile women\textsuperscript{58}. Vinita et al-2003, conducted a cross sectional study on endocrinological factors in reproductive dysfunction, cited a prevalence of thyroid abnormalities in 2.44\% \textsuperscript{59}. In the present study, thyroid abnormalities were prevalent among 2.4\% of infertile women and in 5.2\% of women with pregnancy wastage.

- The overall prevalence of thyroid dysfunction in the present study was 30.8 \% (selective screening of this population has resulted in a higher yield). This correlates with other studies,

Prentice et al- medical management of menorrhagia \textsuperscript{34} – stated 36\% of women with thyroid abnormalities had menstrual dysfunction. In another study by Wilansky et al-1999(early hypothyroidism in menorrhagia) \textsuperscript{29}, had 22\% prevalence among patients with thyroid disorder.

- Our findings for the prevalence of subclinical hypothyroidism are within the expected range for the female population of reproductive age. Prevalence studies have reported incidences between 4 – 10 \%(Mark PG et al 1995) \textsuperscript{60}.

Hollowell JG et al 2002 observed 8.3\% prevalence of subclinical hypothyroidism in their study \textsuperscript{61}. It was observed in our study that 8\% of women with AUB had subclinical hypothyroidism. This should be considered the major benefit of testing because progression rate to overt hypothyroidism is approximately 4\% to 18 \%(Huber G 1998). There are enough data to support the fact that thyroxine replacement in women with subclinical hypothyroidism checks progression.

The prevalence of subclinical hypothyroidism in our study doesn’t correlate with
the 14.6% prevalence in study by Bemben DA 1994(predictability of subclinical hypothyroidism in women)\textsuperscript{62}. Because, in this study the sample population were in the age group 60-97 years. In community surveys 8-17% of people older than 55 years may have subclinical hypothyroidism (Parle JV et al 1991)\textsuperscript{63}.

There is good evidence to support the fact that treatment of patients with subclinical hypothyroidism who have TSH levels $>5$ mIU/L prevents progression to overt hypothyroidism (Surks MI 2004). Failed medical therapy of DUB may be due to underestimate of underlying thyroid disorder.
SUMMARY

The study was undertaken in 250 women with abnormal uterine bleeding in reproductive age group presenting to our tertiary referral hospital. It was done to assess the prevalence and the possibility of a correlation between subclinical thyroid disease and AUB.

A detailed history elicited as per proforma enclosed and anthropometric measurements were taken and a thorough general and systemic examination done. Thyroid function analysis was done in each of these women and the results interpreted.

The mean age of women in the study group was 36 years. There was significant correlation between increasing age and thyroid dysfunction.

A significant correlation with reproductive failure and thyroid abnormalities was cited in the study. Nulliparous women presented earlier with infertility as their primary complaint and statistical significance was also detected in women with reproductive dysfunction.

Women symptomatic of thyroid abnormalities had more incidence of thyroid dysfunction. The symptoms with which they presented were more predictive of the disease. There was also significance between duration of symptoms and presence of thyroid abnormalities. BMI was significantly abnormal more so in patients with hypothyroidism and menorrhagia.

In oligomenorrheic women, thyrotoxicosis was more common with incidence of 94.5% and menorrhagia was observed in 59.2% of hypothyroid women. Women
detected to have subclinical hypothyroidism also presented with menorrhagia (70%) and amenorrhea (25%). Frequency of polymenorrhea and Hypomenorrhea in the study group was relatively low due to the increased incidence of pelvic pathology associated with polymenorrhea. Among 4 women in the study group with Hypomenorrhea and 5 with Polymenorrhea, none had thyroid abnormalities.

In the study group, the overall prevalence of thyroid abnormalities was 30.8%. Among them 15.6% had hypothyroidism and 7.2% had hyperthyroidism and 8% had subclinical hypothyroidism.

**Prevalence:**

Hypothyroidism – 15.6%

Hyperthyroidism – 7.2%

Subclinical hypothyroidism – 8%

The prevalence of preclinical hypothyroidism was 8%. These women had abnormal bleeding of a lesser duration (4-6 months). 13 out of 20 women with subclinical hypothyroidism had symptoms attributable to thyroid dysfunction. Detection of this group of women is considered a major benefit of testing because, supplementation of thyroxine to this group of women will revert back their symptoms and checks progression of their endocrinological disease. All of them had their TSH values between 5 and 8 mIU/L.

Women detected to have overt hypo/hyperthyroidism had longer duration of symptoms and they are now actually detected at a farther end in the spectrum of disease.
after acquiring morbidity in the form of affliction of their quality of life due to the abnormal bleeding and by the onset of anaemia. Hence testing for thyroid function is advocated early in the course of the disease.
CONCLUSION

Our study highlights the following,

- There is significant association between thyroid disorders and abnormal uterine bleeding.

- It brings into focus the increased incidence of hypothyroidism among women with menorrhagia and amenorrhea. And increased incidence of hyperthyroidism in women with oligomenorrhea.

- The prevalence of subclinical hypothyroidism in the study group was 8%.

- It is suggested that women with early onset menorrhagia and oligomenorrhea with or without symptoms & signs attributable to thyroid dysfunction should be offered thyroid function testing to detect them in the subclinical stage.

- Early detection by selective screening and specific pharmacotherapy for subclinical thyroid disease early in the course of the disease will prove to be a superior alternative to surgical treatments like hysterectomy.
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ABBREVIATIONS

AUB – Abnormal Uterine Bleeding
T4 – Thyroxine
T3 – Tri-iodothyronine
TSH – Thyroid Stimulating Hormone.
TRH – Thyrotropin releasing hormone
LH – Leuteinising Hormone.
FSH – Follicle Stimulating Hormone.
hCG – Human Chorionic Gonadotropin.
SHBG – Sex Hormone Binding Globulin.
FT3 – Free tri-iodothyronine
FT4 – Free thyroxine.
TPO – Thyroid peroxidase
BMI – Body Mass Index
IUCD – Intra Uterine Contraceptive Device
PID – Pelvic Inflammatory Disease.
EIA – Enzyme Immuno Assay
SC Hypo – Subclinical hypothyroidism.
PROFORMA
PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN
REPRODUCTIVE AGE GROUP WOMEN WITH ABNORMAL UTERINE
BLEEDING

SERIAL
HOSPITAL NO.: NO:
NAME: OCCUPATION:
AGE:
ADDRESS:
SOCIO-ECONOMIC STATUS:

1. CHIEF COMPLAINTS:

2. HISTORY OF PRESENTING COMPLAINTS:

A) Bleeding per Vagina:
   Duration:
   Interval:
   Quantity: Scanty / Moderate / Excessive
   H/o Dysmenorrhoea: Yes / No

- CLINICAL EVALUATION OF THYROID DISORDER

   Change of Voice: Yes / No
   Weight Gain: Yes / No
   Constipation: Yes / No
   Dryness of Skin: Yes / No
   Cold Intolerance: Yes / No
   Fatigue/Lethargy: Yes / No
   Sleep Disturbance: Yes / No
   Other Details if any:

3. MENSTRUAL HISTORY:

   Acyclical: Yes / No
   Hypomenorrhoea: Yes / No
   Menorrhagia: Yes / No
   Metrorrhagia: Yes / No
   Oligomenorrhea: Yes / No
   Polymenorrhea: 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: Parity:
Abortion: Last child birth:
Type of Deliveries: Tubectomy: Yes / No

5. PAST HISTORY:
HT/DM/TB / Bronchial asthma/ Radiation/Blood transfusion / Any thyroid surgeries

6. FAMILY HISTORY:
TB / Bronchial Asthma / Diabetes mellitus / Hypertension / Any cancer/thyroid illness.

7. PERSONAL HISTORY:
Diet: Appetite: Bowels:
Micturition: Sleep:

EXAMINATION OF PATIENT:
1) General Condition 2) Nutritional Status
3) Anemia 4)BMI 5) CVS/RS/CNS
6) vital signs
7) Breast and Thyroid

8. PER ABDOMEN:
Operative scar: Present / Absent
Engorged vein: Present / Absent
Ascites: Present / Absent
Any enlargement of Liver / Spleen: Palpable / Non Palpable

9. EXTERNAL GENITALIA: Healthy / Non Healthy

10. PER SPECULUM EXAMINATION:
Vagina:
Cervix:
Bleeding: Present / Absent

11. PER VAGINAL EXAMINATION:
Cervix: Normal / Flush with vault
Uterus: Anteverted / Retroverted
Normal size / Bulky/ smaller
Soft / Firm / Hard
Mobile / Fixed
Tender / Non Tender
Tenderness in fornix: Present / Absent

12. Per rectal Examination:

13. INVESTIGATIONS:
• Urine: Albumin/ Sugar/ Microscopy
• BT CT
• Complete hemogram
• Blood sugar, urea, creatinine
• Blood grouping & typing
• Pelvic USG
• Histopathology of Endometrium

**Thyroid Function Test**
- Free T3  - Free T4
- TSH