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# FREQUENCY OF SUBCLINICAL THYROID DISORDERS IN WOMEN OF REPRODUCTIVE AGE GROUP WITH DYSFUNCTIONALL UTERINE BLEEDING

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## ABSTRACT

**Introduction**: Irregularities in the menstrual cycle may accompany or precede clinically overt thyroid dysfunction. Many studies have proved that menorrhagia is more commonly associated with hypothyroidism whereas an ovulation or oligo - menorrhea is common in Hyperthyroidism. Thyroid function test should be routinely investigated in patients presented with DUB in outpatient department to avoid unnecessary invasive procedures. **Objectives:** To determine the frequency of subclinical thyroid dysfunction among patients of menstrual irregularities**. Study Design:** Cross Sectional Study. **Study Duration:** 20th Jan 2022 to 19th July 2022. **Settings:** Department of Obstetrics and Gynaecology, Unit II, Holy Family Hospital, Rawalpindi. **Materials and Methods:** A total of 340 patients with menstrual disturbance of age 18 - 45 years were included. Presence of Palpable Pelvic Pathology, having known Thyroid Disorders, on Drugs like Aspirin, Heparin, Steroids, Amiodarone, Lithium, intrauterine contraceptive devices (IUCS) users, with symptoms of thyroid dysfunctions and on thyroid replacement therapy were excluded. Participants of the study were interviewed for menorrhagia oligomenorrhea, and amenorrhea. Detailed menstrual history and history associated with symptoms of Hypothyroidism and hyperthyroidism was taken. Participants were also clinically examined including GPE, Gentle abdominal, speculum and pervaginal examination. 5mg of venous blood was taken a plain glass tube without any anticoagulant. Morning sample in the fasting state was taken and serum was estimated for TSH, Free T3, Free T4. **Results:** Age range in this study was from 18 to 45 years with mean age of 28.06 ± 4.70 years. Majority of the patients 254 (74.71%) were between 18 to 30 years of age. Mean TSH levels were 4.49 ± 2.21 mI U/l. Frequency of subclinical thyroid dysfunction among patients of menstrual irregularities was found in 95 (27.94%) patients. **Conclusion:** This study concluded that frequency of subclinical thyroid dysfunction among patients of menstrual irregularities is very high**.**

**KEYWORDS:** Dysfunction uterine bleeding, subclinical thyroid dysfunction, menorrhagia.

## INTRODUCTION

Abnormal uterine bleeding/Dysfunctional uterine bleeding is change in menstruation cycle length, regularity, and amount of blood loss/day. It also includes intermenstrual bleeding and postcoital bleeding. The term chronic AUB is defined by FIGO as bleeding from the uterine corpus that is abnormal in volume, regularity and/or timing has been present for the last 6 months.[1] DUB accounts for 10-15% gynaecology related complaints. The causes of abnormal uterine bleeding can be local, systemic and iatrogenic. Local causes include polyp, adenomyosis, leiomyoma, malignancy, endometrial hyperplasia. Systemic causes include coagulopathy disorder and ovulatory disorder secondary to thyroid dysfunction. Among them, the ovulatory disorder is the most common which occurs secondary to thyroid dysfunction.[2]

Thyroid dysfunction is associated with large number of menstrual irregularities. Both hypothyroidism and hyperthyroidism can change reproductive function including delayed onset of puberty, anovulatory cycles.[3] First presentation of hypothyroidism is abnormal blood flow and disturbed menstrual cycle. The occult menorrhagia is an earlier presentation for sub-clinical hypothyroidism. The mechanism by which the thyroid disorders is associated with DUB may be explained by alter:- Ig thyroid stimulating hormone (TSH) response, increasing prolactin levels, altering luteinizing hormone(LH) response, affecting peripheral conversion of androgen to estrogens, altering sex hormone-binding globulin (SHBG) and affecting coagulation pathways in addition to the effect on lipid profile.[4]

A wide spectrum of reproductive disorders ranging from abnormal sexual development, menstrual irregularities, and infertility is linked with hypothyroidism.[5] The

impact of hypothyroidism on the menstrual cycle has been identified since the 1950s and leads to changes in cycle duration and blood flow. Subclinical hypothyroidism has been associated mild disturbances in menstrual amount and duration before becoming symptomatic. The prevalence of subclinical hypothyroidism is as high as 9.5% in women.[6]

Hyperthyroidism before puberty delays, the age of menarche. In fertile age group, oligomenorrhea and amenorrhea are the commonest symptoms of hyperthyroidism. These irregularities sometimes precede thyroid dysfunction.[7] Now a days, hyper- and hypothyroidism can be diagnosed early, these would remain unnoticed few decades ago. The prevalence of sub-clinical hypothyroidism is 5-8 % in adult females and increase up to 20% by the age of 60 years. The early diagnosis and management of thyroid dysfunction is essential for menstrual regularity & fertility.[8]

Abnormal uterine bleeding is a common and complicated entity accounting for almost 20% patients presenting in the outpatient department. Risk of thyroid disorders increases with age and almost 26% of premenopausal and menopausal women are diagnosed with thyroid disease. Thyroid disorders are ten times more common in women than in men possibility due to autoimmune nature of thyroid disease and in older adults compared with younger age groups.[9]

Irregularities in the menstrual cycle may accompany or precede clinically overt thyroid dysfunction. Many studies have proved that menorrhagia is more commonly associated with hypothyroidism whereas an ovulation or oligo-menorrhea is common in Hyperthyroidism.[10] Thyroid function test should be routinely investigated in patients presented with DUB in outpatient department to avoid unnecessary invasive procedures.[11]

Treatment of thyroid abnormalities relives symptoms and has positive effect on female physical health.[12] According to study by Ali et al conducted in Pakistan recently, involving 234 patients of abnormal uterine bleeding and their thyroid status was also assessed which was showing the prevalence of subclinical thyroid dysfunction in 33% of the patients having AUB.[13]

The rationale of study was to determine the menstrual irregularities with subclinical thyroid dysfunction, as thyroid dysfunction may be associated with menstrual irregularities as mentioned above. Timely detection of thyroid disorder in patients presenting with menstrual disorders and their management can prevent unnecessary surgical interventions and morbidity of patients.

## REVIEW OF LITERATURE

### ANATOMY OF UTERUS

The anatomy of the uterus consists of the following 3 tissue layers (figure I).

- The inner layer, called the endometrium, is the most active layer and responds to cyclic ovarian hormone changes; the endometrium is highly specialized and is essential to menstrual and reproductive function.
- The middle layer, or myometrium, makes up most of the uterine volume and is the muscular layer, composed primarily of smooth muscle cells.
- The outer layer of the uterus, the serosa or perimetrium, is a thin layer of tissue made of epithelial cells that envelop the uterus.

The uterus is a dynamic female reproductive organ that is responsible for several reproductive functions, including menses, implantation, gestation, labor, and delivery. It is responsive to the hormonal milieu within the body, which allows adaptation to the different stages of a woman's reproductive life. The uterus adjusts to reflect changes in ovarian steroid production during the menstrual cycle and displays rapid growth and

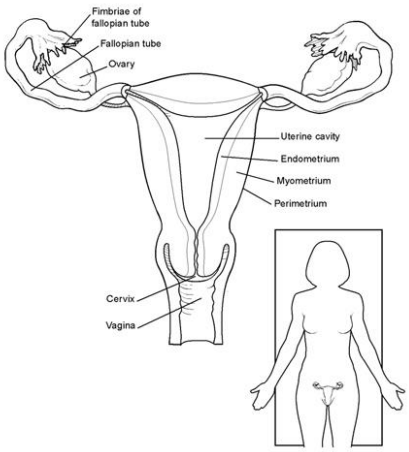


**Figure I: Female reproductive system.**

Specialized contractile activity during pregnancy and child birth. It can also remain in a relatively quiescent state during the prepubertal and postmenopausal years.[14]

### EMBRYOLOGY

The embryonic origin and development of the uterus is relatively complex. Until approximately 8 weeks' gestation, primordia for both male and female internal genitalia the mesonephric (Wolffian) and paramesonephric (Mullerian) ducts, respectively coexist in the embryo. The sexual differentiation process involves multiple steps in which hormonal signals, growth factors, and specific genetic influences are required.

In the female embryo, due to the absence of a Y chromosome and lack of exposure to testosterone from functional testicular tissue, the normal developmental sequence of events results in fusion and canalization of the paramesonephric (Mullerian) ducts in the midline pelvis to form the female pelvic organs. Meanwhile, regression of the mesonephric (Wolffian) ducts occurs. Abnormalities in this process may occur during

embryogenesis, which can result in the range of known paramesonephric anomalies.

**GROSS ANATOMY**

The uterus is a pear-shaped organ located in the female pelvis between the urinary bladder anteriorly and the rectum posteriorly (figure II). The average dimensions are approximately 8 cm long, 5 cm across, and 4 cm thick, with an average volume between 80 and 200 mL. The uterus is divided into 3 main parts: the fundus, body, and cervix.

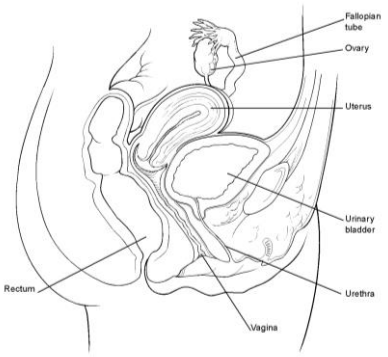


**Figure II: Female pelvis.**

Blood is provided to the uterus by the ovarian and uterine arteries, the latter of which arise from the anterior divisions of the internal iliac artery. The uterine artery occasionally gives off the vaginal artery (although this is usually a separate branch of the internal iliac around), which supplies the upper vagina, and the arcuate arteries, which surround the uterus. It then further branches into the radial arteries, which penetrate the myometrium to provide blood to all layers, including the endometrium (figure III).

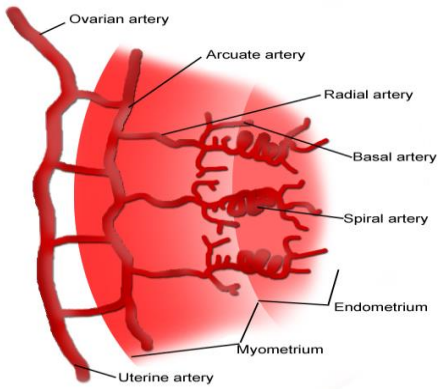


**Figure III: The uterine blood supply.**

Once these vessels reach the endometrial level, they branch into the basal arteries and spiral arteries, which support the specialized functions of each layer. The basal arteries are not responsive to hormones; they support the basal endometrial layer, which provides the proliferative cells for endometrial growth. The spiral arteries supply the functionalis layer and are uniquely sensitive to steroid hormones. In ovulatory cycles in which pregnancy does not occur, menses results following constriction of these terminal arteries, causing endometrial breakdown with desquamation of the glands and stroma.

**Uterine pathologies**

Beyond abnormalities in uterine development, many gynecologic disease processes may affect the uterus. Uterine fibroids, also known as leiomyomas or myomas, are benign smooth muscle tumors that arise in the myometrium of the uterus. These masses can grow within the endometrial cavity of the uterus (submucosal), in the myometrial layer (intramural), or in the outer wall of the uterus (subserosal), or they may extend off the outer layer of the uterus (pedunculated).

Uterine polyps are benign growths on the inner surface of the uterus, derived from local overgrown endometrial tissue. Adenomyosis is a benign condition in which

endometrial tissue invades the myometrial layer of the uterus. It may be focal or diffuse.[14]

Endometrial hyperplasia is an overgrowth of the endometrial tissue within the uterus and may range from simple to complex (in which histology shows glands that are overcrowded and may show precancerous changes).[14]

Endometrial cancer is a malignancy arising from the inner layer of the uterus, the endometrium. Other forms of uterine cancer may involve different tissue layers, such as leiomyosarcoma.

Asherman syndrome is intrauterine scarring or adhesions (synechiae), commonly resulting from damage to endometrium from surgical procedures or infection.

Uterine prolapse is descent of the uterus into the vaginal canal and usually results from weakening of muscles and ligaments of the pelvic floor.

## DYSFUNCTIONAL UTERINE BLEEDING

Dysfunctional uterine bleeding (DUB) is irregular uterine bleeding that occurs in the absence of pathology or medical illness. It reflects a disruption in the normal cyclic pattern of ovulatory hormonal stimulation to the endometrial lining. The bleeding is unpredictable in many ways. It might be excessively heavy or light, prolonged, frequent, or random.

This condition usually is associated with anovulatory menstrual cycles but also can present in patients with oligo-ovulation. DUB occurs without recognizable pelvic pathology, general medical disease, or pregnancy. It is considered a diagnosis of exclusion.[15-18]

## EPIDEMIOLOGY

Dysfunctional uterine bleeding is a common diagnosis, making up 5-10% of cases in the outpatient clinic setting.

### Mortality/Morbidity

Single episodes of anovulatory bleeding generally carry a good prognosis. Patients who experience repetitive episodes might experience significant consequences. Frequent uterine bleeding will increase the risk for iron deficiency anemia. Flow can be copious enough to require hospitalization for fluid management, transfusion, or intravenous hormone therapy. Chronic unopposed estrogenic stimulation of the endometrial lining increases the risk of both endometrial hyperplasia and endometrial carcinoma. Timely and appropriate management will prevent most of these problems.

Many individuals with dysfunctional uterine bleeding are exposed to unnecessary surgical intervention, such as repeated uterine curettage, endometrial ablative therapy, or hysterectomy, before adequate workup and a trial of medical therapy can be completed.

- Iron deficiency anemia: Persistent menstrual disturbances might lead to chronic iron loss in up to 30% of cases. Adolescents might be particularly vulnerable. Up to 20% of patients in this age group presenting with menorrhagia might have a disorder of hemostasis.
- Endometrial adenocarcinoma: About 1-2% of women with improperly managed anovulatory bleeding eventually might develop endometrial cancer.
- Infertility associated with chronic anovulation, with or without excess androgen production, is frequently seen in these patients. Patients with polycystic ovarian syndrome, obesity, chronic hypertension, and insulin-resistant diabetes mellitus particularly are at risk.[19-23]

### Age

Because most cases are associated with anovulatory menstrual cycles, adolescents and perimenopausal women are particularly vulnerable. About 20% of affected individuals are in the adolescent age group, and 50% of affected individuals are aged 40-50 years.

## CAUSES

In ovulatory cycles, progesterone production from the corpus luteum converts estrogen primed proliferative endometrium to secretory endometrium, which sloughs predictably in a cyclic fashion if pregnancy does not occur. Heavy but regular uterine bleeding implies ovulatory bleeding and should not be diagnosed as DUB. Subtle disturbances in endometrial tissue mechanisms, other forms of uterine pathology, or systemic causes might be implicated.

Anovulatory cycles are associated with a variety of bleeding manifestations. Estrogen withdrawal bleeding and estrogen breakthrough bleeding are the most common spontaneous patterns encountered in clinical practice. Iatrogenically induced anovulatory uterine bleeding might occur during treatment with oral contraceptives, progestin-only preparations, or postmenopausal steroid replacement therapy.

- **Estrogen breakthrough bleeding**
  - Anovulatory cycles have no corpus luteal formation. Progesterone is not produced. The endometrium continues to proliferate under the influence of unopposed estrogen.
  - Eventually, this out-of-phase endometrium is shed in an irregular manner that might be prolonged and heavy. This pattern is known as estrogen breakthrough bleeding and occurs in the absence of estrogen decline.

- **Estrogen withdrawal bleeding**
  - This frequently occurs in women approaching the end of reproductive life.
  - In older women, the mean length of menstrual cycle is shortened significantly due to aberrant follicular

recruitment, resulting in a shortened proliferative phase. Ovarian follicles in these women secrete less estradiol. Fluctuating estradiol levels might lead to insufficient endometrial proliferation with irregular menstrual shedding. This bleeding might be experienced as light, irregular spotting.
- Eventually, the duration of the luteal phase shortens, and, finally, ovulation stops. Dyssynchronous endometrial histology with irregular menstrual shedding and eventual amenorrhea result.

- **Oral contraceptives, progestin-only preparations, or postmenopausal steroid replacement therapy**
- Treatment with oral contraceptives, progestin-only preparations, or postmenopausal steroid replacement therapy might be associated with iatrogenically induced uterine bleeding.
- Progesterone breakthrough bleeding occurs in the presence of an unfavorably high ratio of progestin to estrogen.
- Intermittent bleeding of variable duration can occur with progestin-only oral contraceptives, depo-medroxyprogesterone, and depo-levonorgestrel.
- Progesterone withdrawal bleeding can occur if the endometrium initially has been primed with endogenous or exogenous estrogen, exposed to progestin, and then withdrawn from progestin. Such a pattern is seen in cyclic hormonal replacement therapy.[24]

- **Adolescents**
- The primary defect in the anovulatory bleeding of adolescents is failure to mount an ovulatory luteinizing hormone (LH) surge in response to rising estradiol levels. Failure occurs secondary to delayed maturation of the hypothalamic-pituitary axis. Because a corpus luteum is not formed, progesterone levels remain low.
- The existing estrogen primed endometrium does not become secretory. Instead, the endometrium continues to proliferate under the influence of unopposed estrogen. Eventually, this out-of-phase endometrium is shed in an irregular manner that might be prolonged and heavy, such as that seen in estrogen breakthrough bleeding.

- **Climacteric**
- Anovulatory bleeding in menopausal transition is related to declining ovarian follicular function.
- Estradiol levels will vary with the quality and state of follicular recruitment and growth.
- Bleeding might be light or heavy depending on the individual cycle response.

- **Bleeding disorders:** An international expert panel including obstetrician/gynecologists and hematologists has issued guidelines to assist physicians in better recognizing bleeding disorders, such as von Willebrand disease, as a cause of menorrhagia and postpartum hemorrhage and to provide disease-specific therapy for the bleeding disorder.[25] Historically, a lack of awareness of underlying bleeding disorders has led to under diagnosis in women with abnormal reproductive tract bleeding. The panel provided expert consensus recommendations on how to identify, confirm, and manage a bleeding disorder. An underlying bleeding disorder should be considered when a patient has any of the following.

- Menorrhagia since menarche
- Family history of bleeding disorders
- Personal history of 1 or more of the following
  - Notable bruising without known injury
  - Bleeding of oral cavity or gastrointestinal tract without obvious lesion
  - Epistaxis greater than 10 minutes duration (possibly necessitating packing or cautery)
- If a bleeding disorder is suspected, consultation with a hematologist is suggested.

## PATHOPHYSIOLOGY

### Mechanism of normal menstruation

The seat of normal menstrual bleeding is located in the upper two-thirds of the endometrial mucosa. It is characterized by tissue necrosis, disruption of microvasculature, migratory leukocytes, and platelet/fibrin thrombi in microvessels.[31] Menstruation is initiated by the enzymatic degradation of the endometrium as a result of estrogenprogesterone withdrawal. In the first half of the secretory phase of the menstrual cycle, acid phosphatase, and other potent lytic enzymes are confined to lysosomes. The release of these enzymes is inhibited by progesterone which stabilizes the lysosomal membranes. During the second half of the secretory phase, due to the withdrawal of estradiol and progesterone, the enzymes are released into the cytoplasmic substance and intercellular space. In the vascular endothelium lytic-enzyme release leads to platelet deposition, release of prostaglandins, vascular thrombosis, extravasation of red blood cells, and tissue necrosis.[26] In addition, the withdrawal of progesterone up-regulates key inflammatory mediators. Among the stimulated agents the α-chemokine CXCL8 (neutrophil chemotactic factor, IL-8) and the α-chemokine CCL-2 (monocyte chemotactic peptide-1, MCP-1), as well as the inducible enzyme, COX-2 are responsible for the synthesis of prostaglandins.[27]

Immediately before and during menstruation, there is the induction of the expression, secretion, and activation of matrix metalloproteinases which have the capacity to degrade all of the components of extracellular matrix.[28] Progesterone inhibits endometrial metalloproteinase expression, an action mediated by transforming growth factor-α.[29] As a result of progesterone withdrawal, metalloproteinase secretion and activation are increased, followed by dissolution of the extracellular matrix. The enzymatic degradation of endometrium extends to the deepest extent of functional layer, where the rupture of

basal arterioles contribute to bleeding that caused by the dissolution of the surface membrane. A cleavage plane develops at the junction of the loose, vascular, edematous stroma with the basal layer. Desquamation begins in the fundus and gradually extends towards the isthmus.[30]

Immediately after separation of the functional layer of the endometrium, endometrial regeneration and vessel growth are initiated by the influence of estradiol. TGF-α, EGF, and platelet derived growth factor (PDGF) are mitogens for epithelial cells that origin from the basal layer.[31] Vascular endothelial growth factor (VEGF) together with FGF and PDGF are known to stimulate angiogenesis in the endometrium.[32] Early in menstruation the hemostasis is provided by platelet and fibrin plug formation. However, the cessation of menstrual bleeding depends on vasoconstriction of the denuded spiral arterioles in the basal layer and possibly of the radial arteries of superficial myometrium, an action that is promoted by endothelins and prostaglandins in the menstrual endometrium.[26]

**Mechanism of dysfunctional uterine bleeding**

There are two types of dysfunctional uterine bleeding; ovulatory (10%) and anovulatory (90%). In ovulatory cycles the menstrual pattern is uniform, regular and heavy but of normal duration. On the contrary, in anovulatory cycles the pattern is variable, irregular and the duration may be longer.[30] Ovulatory dysfunctional uterine bleeding is the major pattern in 30s, whereas anovulatory dysfunctional uterine bleeding is more likely to occur at the extremes of reproductive years and in women who have polycystic ovarian syndrome.

In ovulatory dysfunctional uterine bleeding, generally circulating ovarian hormone levels are normal and endometrial histology shows changes identical to women without dysfunctional uterine bleeding. Therefore, the major proposed mechanism of ovulatory dysfunctional uterine bleeding is impaired hemostatic mechanisms. A shift in the ratio of endometrial vasoconstrictor (PGF2α) to vasodilator (PGE2), and an increase in total endometrial prostaglandins have been demonstrated in ovulatory dysfunctional uterine bleeding patients.[31] Platelet and plug formation are poor due to prolonged vasodilation. In addition, a potent vasodilator parathyroid hormone- related protein and high proteolytic lysosomal enzyme activity are increased in women with ovulatory dysfunctional uterine bleeding.[33] As a result, in ovulatory dysfunctional uterine bleeding, treatment with prostaglandin synthetase inhibitors are more effective than hormonal treatment. However, there are rare hormonal conditions that cause abnormal uterine bleeding in ovulatory cycles. The most common one is midcycle bleeding due to abrupt fall in estrogen levels just before the ovulation which is called as 'estrogen withdrawal bleeding'. Another one is the luteal phase defect which is characterized by spotting before the menstruation because of insufficient progesterone secretion, and known as 'progesterone withdrawal bleeding'.

Anovulatory dysfunctional bleeding occurs as a result of endometrial response to abnormal levels of steroid hormones. As normal menstruation results from estrogen-progesterone withdrawal, hyperestrogenic or hyperprogestogenic states end with anovulatory bleeding.

While estrogen is the principal hormone which is effective on the endometrial glands and vasculature, progesterone mainly affects the stroma. In normal menstruation cycle, estrogen and progesterone stimulus is balanced leading to stable endometrial epithelium, stroma, and microvasculature. Random breakdown is avoided, and endometrial shedding occurs uniformly throughout the endometrial cavity. Prolonged hyperestrogenism unopposed by progesterone, leads to proliferative endometrium and hyperplasia with a poor stromal matrix.[26] The bleeding caused by focal stromal breakdown is called 'estrogen breakthrough bleeding'. Endometrial shedding is irregular, and not universal. There is constantly changing patchwork of small repairs instead of organized and well structured remodeling. In persistent proliferative endometrium, spiral arterioles are often suppressed and venous capillaries are dilated and increased in number.[26] Also, the sensitivity of abnormal vasculature in hyperestrogenic endometrium is suspected to be greater to vasodilation by prostaglandins than to their vasoconstrictor counterparts.[34] In addition, a potent vasoconstrictor, angiotensin-2 is decreased in endometrial hyperplasia. Anovulatory dysfunctional uterine bleeding is initiated by an increase in vascular density with abnormal structural abnormalities leading to rupture or degradation of the microvascular system.[26] As tissue loss involves the superficial endometrium only focally, vasoconstriction of basal and radial arteries does not occur and this causes abnormalities in hemostasis. This is the mechanism of bleeding in chronic anovulation. The amount and duration of bleeding can vary according to the amount and duration of unopposed estrogen exposure.[30] Low level chronic estrogen stimulation typically results in intermittent spotting, whereas sustained high level estrogen exposure commonly results in acute episodes of profuse bleeding.

Anovulatory dysfunctional uterine bleeding due to hyperprogestogenism, known as 'progesterone breakthrough bleeding' manifests in continuous progestin or low-dose oral contraceptive users. Endometrial histology is chiefly influenced by progesterone and ranges from severe atrophy with or without stromal decidualization to mixed proliferative/secretory patterns according to the duration and amount of progesterone exposure.[26] As the progesterone/estrogen ratio increases, secretory-type atrophy becomes prominent with a gland-stroma ratio largely in favour of the stroma.

Histologically there is a decrease in the number and tortuosity of spiral arterioles and many of the sub epithelial micro vessels are dilated and lined by a very thin endothelial cell layer.[35] Since the basement membrane is poorly formed or absent, and there are gaps between endothelial cells, pools of extravasated red blood cells are often seen.[36] These structural alterations and vascular fragility lead to breakdown and bleeding.

## PRESENTATION

### History

- Suspect dysfunctional uterine bleeding (DUB) when a patient presents with unpredictable or episodic heavy or light bleeding despite a normal pelvic examination.
  - Typically, the usual moliminal symptoms that accompany ovulatory cycles will not precede bleeding episodes.
  - Exclude the diagnosis of pregnancy first.
  - Address the presence of local and systemic disease. Rule out the presence of signs or symptoms indicative of bleeding disorders. Screening for personal and family history of easy bruising, bleeding gums, epistaxis, and excessive bleeding episodes during childbirth, surgery, or dental procedures may be useful.
  - Rule out iatrogenic causes of bleeding, including bleeding secondary to steroid hormone contraception, hormone replacement therapy, or other hormone treatments, which are common causes.
  - Most patients are adolescents or are older than 40 years.

- Patients who report irregular menses since menarche may have polycystic ovarian syndrome (PCOS). PCOS is characterized by anovulation or oligo-ovulation and hyperandrogenism. These patients often present with unpredictable cycles and/or infertility, hirsutism with or without hyperinsulinemia, and obesity.
- Patients with adrenal enzyme defects, hyperprolactinemia, thyroid disease, or other metabolic disorders also might present with anovulatory bleeding.

### Physical

The physical examination can elicit several anatomic and organic causes of abnormal uterine bleeding.

- A complete physical examination should begin with assessment of hemodynamic stability (vital signs) and proceed with evaluation of the following.
  - Obesity (BMI)
  - Signs of androgen excess (hirsutism, acne)
  - Thyroid enlargement or manifestations of hyperthyroidism or hypothyroidism.
  - Galactorrhea (may suggest hyperprolactinemia).
  - Visual field deficits (raise suspicion of intracranial/pituitary lesion).
  - Ecchymosis, purpura (signs of bleeding disorder).
  - Signs of anemia or chronic blood loss.

- A careful gynecologic examination, including Papanicolaou test (Pap smear) and sexually transmitted disease (STD) screening, is warranted.
- The hallmark of DUB is a negative pelvic examination despite the clinical history. In such cases, management might rest on a clinical diagnosis.
  - Rule out the presence of uterine fibroids or polyps.
  - Rule out endometrial hyperplasia or carcinoma.

## DIFFERENTIAL DIAGNOSES

- Abortion
- Adnexal Tumors
- Cervical Cancer
- Cervicitis
- Chlamydial Genitourinary Infections
- Ectopic Pregnancy
- Endometrial Carcinoma
- Endometriosis
- Endometritis
- Gestational Trophoblastic Neoplasia
- Hyperprolactinemia
- Hyperthyroidism
- Hypothyroidism
- Ovarian Polycystic Disease
- Uterine Cancer
- Vaginitis

## DIAGNOSIS

- **Laboratory Studies**
  Laboratory studies for patients with dysfunctional uterine bleeding (DUB) include human chorionic gonadotropin (HCG), complete blood count (CBC), Pap smear, endometrial sampling, thyroid functions and prolactin, liver functions, coagulation studies/factors, and other hormone assays as indicated.

- **Human chorionic gonadotropin**
  - The most common cause of abnormal uterine bleeding during the reproductive years is abnormal pregnancy.
  - Rule out threatened abortion, incomplete abortion, and ectopic pregnancy.

- **Complete blood count**
  - Document blood loss. Charting the number of menstrual pads used per day or keeping a menstrual calendar is helpful.
  - When in doubt, obtain a baseline CBC count for hemoglobin and hematocrit.
  - Rule out anemia.
  - Obtain a differential with platelet count if hematologic disease is suspected.
- Pap smear should be up to date. Cervical cancer still is the most common gynecologic cancer affecting women of reproductive age in the world population.

- **Endometrial sampling**
  - Perform a biopsy to rule out endometrial hyperplasia or cancer in high-risk women >35 years and in younger women at extreme risk for endometrial hyperplasia/carcinoma. Women with chronic eugonadal anovulation, obesity, hirsutism, diabetes, or chronic hypertension are at particular risk.
  - Most biopsies will confirm the absence of secretory endometrium.
- Perform thyroid function tests and prolactin because hyperthyroidism, hypothyroidism, and hyperprolactinemia are associated with ovulatory dysfunction. Identify and treat these conditions.
- Obtain liver function tests if alcoholism or hepatitis is suspected. Any condition affecting liver metabolism of estrogen can be associated with abnormal uterine bleeding.

- **Coagulation factors**
  - Von Willebrand disease and factor XI deficiency initially might manifest during adolescence.
  - Primary or secondary thrombocytopenia can be factors in the mature patient.
  - Tailor the choice of laboratory tests to the presenting clinical situation. Generally speaking, when coagulopathies are present, heavy bleeding is regular (menorrhagia) and associated with ovulation.

- **Other hormone assays as indicated**
  - For the patient with recurrent anovulatory bleeding, the mainstay of management is treatment of correctable disease.
  - Obtain a hormonal complete evaluation in women with signs of hyperandrogenism, such as those with polycystic ovarian syndrome, 21 hydroxylase deficiency, or ovarian or adrenal tumors, as dictated by their respective conditions.
  - Women in menopausal transition usually can be followed without an extensive hormonal evaluation.

- **Imaging Studies**
  - Generally, patients with DUB can be managed appropriately without the use of expensive imaging studies.
  - In obese patients with suboptimal pelvic examination or in patients with suspected ovarian or uterine pathology, pelvic ultrasonographic evaluation might be helpful.
  - Ultrasound can be used to examine the status of the endometrium. Endometrial hyperplasia, endometrial carcinoma, endometrial polyps, and uterine fibroids can be identified easily by this technology.

- **Procedures**
- Rule out endometrial carcinoma in all patients at high risk for the condition, including patients with the following characteristics.
  - Morbid obesity.
  - Diabetes or chronic hypertension.
  - Age >35 years.
  - Longstanding, chronic eugonadal anovulation.
- Traditionally, carcinoma was ruled out by endometrial sampling via dilation and curettage (D&C). More recently, endometrial sampling in the office via aspiration, curetting, or hysteroscopy has become popular and is also relatively accurate.
- Real-time ultrasound measurement and evaluation of the endometrial stripe can be helpful in distinguishing individuals bleeding with thick endometrium from those with thin, denuded endometrium, endometrial polyps, uterine fibroids, or other uterine pathology.
- Saline-infusion sonohysterography is also very useful in evaluating for intracavitary (submucosal) fibroids and endometrial polyps.

- **Histologic Findings**

Most endometrial biopsy specimens will show proliferative or dyssynchronous endometrium.

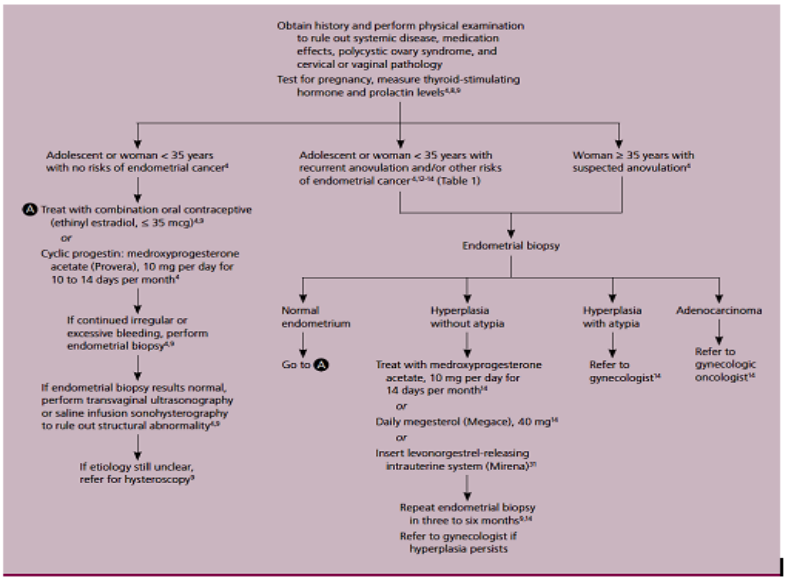


**Figure IV: Evaluation and Treatment of Anovulatory Dysfunctional Uterine Bleeding.**

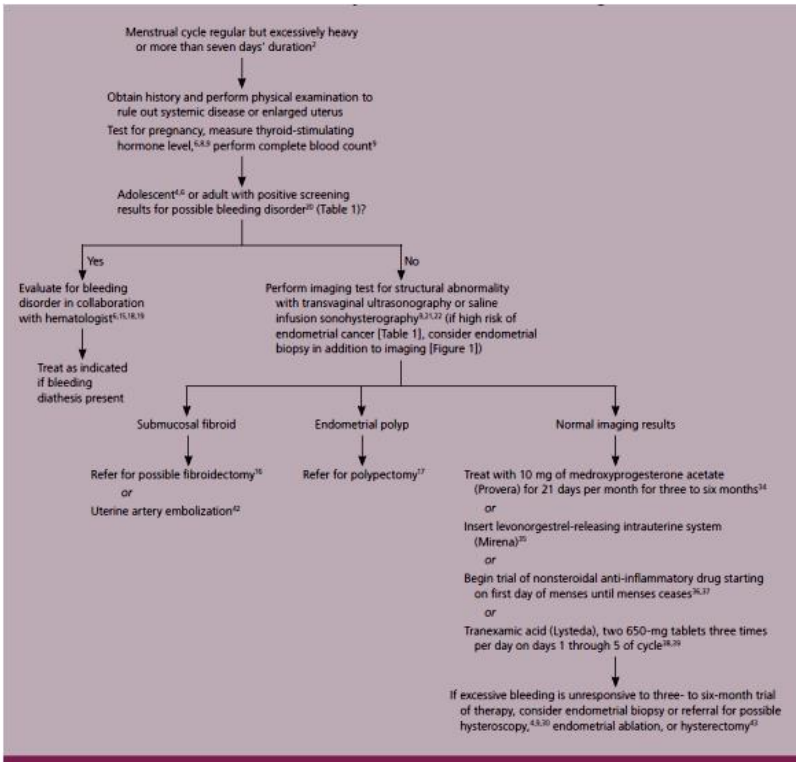


**Figure V: Evaluation and Treatment of Ovulatory Dysfunctional Uterine Bleeding.**

## TREATMENT

Options for medical care of dysfunctional uterine bleeding usually involve various protocols of estrogen or progesterone supplementation, yet there is no clear consensus on which exact regimen is most effective.[37] Medical therapy options are as follows.

### Hormonal medical treatment

If anovulation is strongly suspected as the cause of abnormal bleeding, after pregnancy is ruled out, empiric medical management can be initiated with the expectation of improvement in a short amount of time. If the abnormal bleeding does not improve, further evaluation is necessary before increasing the dosage or changing to another regimen. If other disorders, such as uterine pathology or coagulopathy, are suspected, laboratory testing, endometrial biopsy, and radiographic imaging should be performed before medical management.

The goal of treatment for dysfunctional uterine bleeding is to restore the natural cycle of orderly endometrial growth and shedding. Cyclic progestin therapy works well in women who are completely anovulatory by restoring the normal sequence of steroid stimulation to the endometrium: estrogen, followed by estrogen and progestin, followed by withdrawal. Orderly withdrawal bleeding can be induced by use of a progestin such as medroxyprogesterone acetate, 5 to 10 mg daily, for 2 weeks every month. The interval can be fixed to the calendar by beginning on a specific day of the month (i.e. the first of every month) or at the onset of menses (beginning day 15 or 16 after the first day of the last progestin-induced menses). If menses does not follow progestin withdrawal, pregnancy or hypoestrogenic disorders should be considered.

Cyclic progestins are typically efficacious for anovulatory women; however, in women who still occasionally ovulate and do not want to conceive, a combined oral contraceptive is a better option. Cyclic progestin therapy does not suppress the hypothalamic-pituitary-ovarian axis enough to prevent ovulation. When women ovulate intermittently, the treatment may not coincide with endogenous progesterone production and may lead to bleeding that does not correlate with the predicted pattern. On the other hand, because they suppress endogenous hormone production, combined oral contraceptives should prevent this from occurring. Oral contraceptives also increase sex-hormone binding globulin, which further reduces bioavailable androgens in women with hyperandrogenic anovulation.[38] Oral contraceptives also reduce menstrual flow in women with heavy menstrual flow, even if fibroids or adenomyosis is present.[39] The transdermal contraceptive patch and the vaginal ring can be used in a similar fashion.

Cyclic progestin supplementation in the luteal phase also has been used with some success for women with menorrhagia. The results lead to decrease in menstrual blood flow, but it is often not well tolerated because of gastrointestinal side effects and weight gain. Longer durations of progestin treatment can be used with an even greater decrease in menstrual blood loss, but they

are not as effective or as well tolerated as other regimens, such as the progestin intrauterine device (IUD).[40]

In women who present with episodes of heavy bleeding, combined estrogen- progestin treatment is the best option. To slow or stop a heavy bleed, a ‘‘taper’’ can be performed with any of the low-dose monophasic pills.

Treatment regimens vary but often begin with three pills per day for 3 days, followed by two pills per day for 3 days, and then one pill per day thereafter until the placebo week. The patient can be told to skip the initial placebo week and proceed straight through to a second pill pack to prolong the relief from bleeding. Bleeding slows or stops within 24 to 48 hours, but high-dose levels of hormone should be maintained for the initial 5 to 7 days.

Women often experience nausea and vomiting with the initial ‘‘boost’’ of hormones; prescribing an antiemetic for use during this time should be considered. If there is contraindication to estrogen, progestin can be used instead, but high doses are usually needed (medroxyprogesterone, 20 mg, or norethindrone, 5 mg, daily). If either treatment fails, further diagnostic evaluation is required.

For the short-term, the decidual changes induced by the aforementioned treatments provide stability to a fragile, overgrown endometrium. Unfortunately, a substantial amount of tissue still may remain to be shed once treatment is stopped. The patient should be informed to expect a heavy, painful bleeding within 2 to 4 days after treatment is withdrawn or during the ‘‘placebo’’ week of her pills. Maintenance therapy with a cyclic combination contraceptive (pill, transdermal patch, or vaginal ring) can begin after the initial withdrawal bleed, and each successful menses should be lighter and less painful. If treatment is not continued and the pathophysiology underlying the chronic anovulation is not resolved, heavy or prolonged bleeding is likely to recur.

Another alternative for maintenance therapy is depot-medroxyprogesterone acetate (Depo-Provera), 150 mg intramuscularly, every 3 months. It can be used for women who have contraindication to estrogen or suffer side effects that prevent estrogen use. Although this regimen cannot be used in the setting of acute heavy bleeding, it eventually leads to a thin endometrium.

Some patients experience episodic breakthrough bleeding while on Depo-Provera when the progesterone effect outweighs the estrogen effect on the endometrium. When this occurs, intermittent bleeding can occur (usually light), and it is commonly treated with short courses of estrogen.

Low-dose courses of estrogen can be used when bleeding occurs from an attenuated or grossly denuded endometrium. Ultrasound can help distinguish when this is the case with visualization of an endometrium less than 4 mm in thickness. This is commonly seen when breakthrough bleeding occurs with low-dose contraceptive pills, progesterone-only contraceptives, Depo-Provera, or progestin implants, such as the etonorgestrel implant (Implanon). In these patients, the progestin thins the endometrium to atrophic levels, which results in light spotting or staining unless there is sufficient endogenous or exogenous estrogen to effectively balance its effects. These lesser, lighter bleeds respond to a single, daily dose of estrogen (e.g. 1.25 mg conjugated estrogens for 7–10 days). If treatment fails, further evaluation is recommended with ultrasound or saline sonohysterography to identify a causative polyp or myoma. If no anatomic cause is found, changing the dose or type of contraceptive is indicated.

Occasionally patients present with acute, heavy, active bleeding that may require inpatient treatment and close observation. In these cases, high-dose estrogen is used because it promotes rapid endometrial growth and covers denuded endometrial surfaces. Intravenous estrogen (25 mg conjugated equine estrogens every 4 hours for 24 hours or until bleeding diminishes significantly) is the usual regimen and has been shown to be successful in most cases.[41] In the rare case that a woman presents with hemodynamic instability and acute bleeding, or if bleeding does not respond to the first two doses of intravenous estrogen, intrauterine Foley bulb placement or operative hysteroscopy with dilation and curettage is indicated.[42]

When bleeding is heavy but does not require inpatient treatment, oral estrogens can be used as an alternative (1.25 mg conjugated estrogens or 2.0 mg micronized estradiol every 4–6 hours for 24 hours). Gradual tapering is performed down to one dose per day for 7 to 10 days after the bleeding is controlled. All of these initial estrogen treatments should be followed by progestin treatment or combination contraceptives to stabilize the estrogen- stimulated endometrial growth.

Importantly, elevated doses of estrogen (more than one oral contraceptive per day or several doses of oral or intravenous estrogen in 24 hours) can increase the risk of thromboembolism. It is difficult to quantify the absolute risk associated with these short-term courses of high-dose estrogen. In general, low doses of estrogen for short periods of time pose little additional risk, even in women with risk factors; however, in women with history of thrombosis or a family history of thromboembolism, high doses should be avoided if possible. In the end, the decision to use the treatment should be made after the benefits of the treatment are weighed against the risks and alternatives are considered.

**Alternative hormonal management**

For many patients, alternate methods of combined hormone treatment can be used in place of traditional oral contraceptives. The transdermal or vaginal

administration of estrogen and progestin is a more attractive alternative because of less frequent dosing and more stable circulating levels of hormones. There is improved compliance with these methods with elimination of the timed daily dosage and elimination of some of the side effects associated with oral medication. Theoretically, there might also be an advantage to removal of the first-pass effect in the liver.

The transdermal patch (Ortho Evra) delivers 20 mg ethinyl estradiol and 150 mg norelgestromin when applied to locations on the torso and upper arm.[43] The serum concentrations are in ranges equivalent to an oral formulation of 35 mg ethinyl estradiol and 250 mg norelgestromin; however, the kinetics differ secondary to avoidance of daily fluctuations that are experienced when using pills. As a result, systemic steady state hormone levels are 60% higher and peak concentrations are 35% lower.[44] The patch is to be worn for a week, followed by removal and application of a new patch on a different site for another week. After 3 weeks of use, no patch is worn on the fourth week, which leads to a withdrawal menses. The patch also can be used continuously, which eliminates the withdrawal week (and thus menses), until a later time. Break though bleeding occurs in some women on continuous therapy. A small percentage of women also have problems with detachment, local skin reactions, breast discomfort, and nausea and vomiting.[44]

Recent attention to the thromboembolic risk associated with the patch has led to concern regarding its use. Epidemiologic, case control studies have been performed using health care claims data to evaluate the risk of venous thromboembolism among women who used the patch compared with women who used oral contraceptives that contained 35 mg of ethinyl estradiol and norgestimate. These studies used slightly different designs and reported odds ratios ranging from 0.9 to 2.4.[45-47] Until further study is done, the patch has the same absolute and relative contraindications as a combined oral contraceptive pill.

The vaginal contraceptive ring (NuvaRing) consists of a flexible, soft, transparent ring that contains etonorgestrel and ethinyl estradiol. The ring is made as ‘‘one size fits all’’ and releases 15 mg ethinyl estradiol and 120 mg etonorgestrel per day.[44] The hormone levels reach maximum levels 7 days after insertion and remain stable for 35 days without much fluctuation.[44] The patient self-inserts the ring into the vagina and wears it for 3 weeks.

Removal in the fourth week leads to a withdrawal menses, after which the patient inserts a new ring. Continuous use is also an effective option, and it allows menstrual bleeding to be postponed, with breakthrough bleeding as a possible side effect. Estradiol exposure is 3.4 times lower with the ring than the patch and 2.1 times lower than in pill users; however, it still effectively inhibits ovulation.[44] This is likely the reason for fewer estrogenic side effects, such as nausea and breast tenderness. Discontinuation generally occurs because of vaginal discomfort or sensation of the ring in place, problems with intercourse, or expulsion. Insertion and removal are generally easy, and even if the ring is felt during intercourse, this is not a usual reason for discontinuation.

The levonorgestrel IUD (Mirena) is the only progestin-releasing IUD available in the United States, and it is approved for 5 years of use. Menstrual blood loss can be reduced approximately 75% to 95% with Mirena in place and it seems to be superior to other treatments for menorrhagia, such as cyclic progestins. When compared with ablation, although amenorrhea is achieved less frequently, women were equally satisfied.[48]

The use of gonadotropin-releasing hormone agonist (GnRHa), such as leuprolide acetate, can achieve short-term relief of bleeding and is often used to ‘‘bridge’’ women to surgical treatment such as ablation, myomectomy, and hysterectomy for abnormal uterine bleeding. The amenorrhea achieved by use of GnRHa provides relief of bleeding, which allows hemoglobin levels to rise and decreases the risk of transfusion in subsequent surgery.[49,50] GnRHa also decreases the size of fibroids by as much as 35% to 65%, which may allow a vaginal route for a hysterectomy that otherwise may have had to be performed abdominally.[49,50] When myomectomy is the planned procedure, GnRHa decreases the need for a vertical incision and lowers operative blood loss but may lead to difficulty with assessing tissue planes around the fibroids.[49] The thinning effect of the endometrium caused by GnRH agonists can improve visualization during hysteroscopy and may improve the short-term outcome of endometrial ablation.[51] Because of the high cost, effect on bone density, and other side effects from estrogen deficiency (e.g. hot flashes and night sweats), long-term use of these medications is not generally recommended.

**Nonhormonal medical treatments**

**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

The endometrium of women with menorrhagia has been found to have higher levels of PGE2 and F2a when compared with normal menses.[52] Also, the ratio of prostaglandin E2 to F2, and the ratio of prostaglandin I2 to thromboxane are elevated resulting in deranged hemostasis.[39] Nonsteroidal anti-inflammatory drugs inhibiting prostaglandin synthesis by the enzyme cyclo-oxgenase, reduce the menstrual blood loss approximately 20-40% and to a greater extent in those with excessive bleeding.[53]

Mefenamic acid, naproxen, ibuprofen, flurbiprofen, meclofenamic acid, diclofenac, indomethacin and asetylsalicyclic acid are used for the treatment of heavy menstrual bleeding. There are no differences in clinical efficiency between individual prostaglandin inhibitors. However, there are some women who seem to respond

well to one agent but less well to another.[54] As a group, Nonsteroidal anti-inflammatory drugs are less effective than tranexamic acid, danazol and levonorgestrel releasing intrauterine system, whereas there was no significant difference in efficacy in comparison with oral luteal progestogen, ethamsylate, and oral contraceptive pill.[54]

The advantage of this treatment is the low incidence of side effects as the drug is used only during the bleeding period. Also, it provides relief from dysmenorrhea which is often related to heavy menstrual bleeding. Side effects of nonsteroidal anti-inflammatory drugs include headache and gastroinstestinal symptoms such as nausea, vomiting, diarrhea and dyspepsia. Contraindications are gastrointestinal disorders such as ulcers, intolerance to nonsteroidal anti-inflammatory drugs, or asthma.[55]

**Tranexamic acid**

Tranexamic acid is an anti-fibrinolytic. Plasminogen activators, the enzymes that cause fibrinolysis, are found in higher levels in the endometrium of women with heavy menstrual bleeding than those with normal menstrual bleeding.[56] Thus, anti-fibrinolytic drugs are used in the treatment of menorrhagia. Tranexamic acid is more effective than either nonsteroidal anti-inflammatory drugs and oral luteal phase progestogens.[53] Also the studies comparing tranexamic acid with oral progestogens for changes in quality of life showed that the former is more effective in improving flooding and leakage problems and sex life.[48] It is prescribed on only the heavy days of the menses, with a dose of 1 g 3-4 times daily.[55] However, in a study a dose of 2g/day is shown to be more effective than 10 mg twice-daily medroxyprogesterone acetate.[57] Tranexamic acid may be considered as a first-line treatment for ovulatory dysfunctional uterine bleeding, especially for patients in whom hormonal treatment is either not recommended or not wanted.[58]

Although it is known to reduce the menstrual blood loss by 50%,[59] tranexamic acid has not been used widely because of its possible side effects. Since it is an anti-fibrinolytic drug, it is suggested to be associated with thrombogenic disease. However, the studies were unable to show increased rates of thrombogenic disease with tranexamic acid administration in comparison to placebo.[60] The recent studies proved that tranexamic acid is an effective and safe form of medical therapy in women with menorrhagia without any serious adverse effects.[57,61]

Eythamsylate is a drug used rarely in heavy menstrual bleeding. Even though it is not a true anti-fibrinolytic, it affects in a similar mechanism. It reduces capillary bleeding by correcting abnormal platelet function.[48]

**Levonorgestrel-releasing intrauterine system**

Levonorgestrel-releasing intrauterine system has been developed primarily as a contraceptive device which does not suppress ovulation. It consists of a T-shaped intrauterine device sheated with a reservoir of levonorgestrel that is released at the rate of 20 µg daily. This low level of hormone minimizes the systemic progestogenic effects, and patients are more likely to continue with this therapy than with cyclical progestogen therapy. It prevents the endometrial proliferation and reduces both the duration and amount of bleeding.[62] It is accepted as an alternative to surgery with a reduction in menstrual blood loss up to 90%.[63] It is more effective than the other medical therapies.[64] A study comparing the efficacy of levonorgestrel-releasing intrauterine system to oral contraceptives, showed a more pronunced clinical benefit with levonorgestrel-releasing intrauterine system therapy in terms of decreasing menstrual blood loss score after 6 months of treatment.[65] This is a more acceptable treatment than norethisterone taken for 21 days of the cycle for the women, and they are more satisfied with this therapy. Levonorgestrel-releasing intrauterine system treatment has been compared to either transcervical resection of the endometrium or balloon ablation.[64] Although there was a higher rate of successful treatment in those undergoing transcervical resection or balloon ablation in four trials, rates of satisfaction and change in quality of life were similar, but women with levonorgestrel-releasing intrauterine system had a greater incidence of progestogenic side effects within a year. In two studies, 82% and 64% of women on a waiting list of hysterectomy cancelled their surgery after using levonorgestrel-releasing intrauterine system. Another study comparing levonorgestrel-releasing intrauterine system with hysterectomy, revealed that there was no significant difference in quality of life scores, but the former treatment had lower costs than the latter.[66]

Side effects are ectopic pregnancy, expulsion of device and progestogenic effects such as bloating, weight gain and breast tenderness.[64] Irregular bleeding and spotting are temporary and generally seen in the first three months. However, after 12 months of therapy, there is a major reduction in blood loss up to 97%, thus, most of the women have a light bleeding and 20% of them have amenorrhea. As amenorrhea and altered bleeding patterns may be undesirable to some women, counseling before insertion is very important. Relief from dysmenorrhea and reduced incidence of pelvic inflammatory disease due to the thickening of the utero-cervical mucus are additional advantages of levonorgestrel-releasing intrauterine system. An increased incidence of transient ovarian cysts has been reported with levonorgestrel releasing intrauterine system use.[67]

Due to its high efficacy in reducing menstrual blood loss without disturbing fertility, this method offers a first-line therapy for dysfunctional uterine bleeding in women of any reproductive age who wish a contraceptive method and accept hormonal drug use.

**Endometrial hyperplasia**

Endometrial hyperplasia is a possible consequence of chronic anovulation and is categorized as ‘‘simple’’ or ‘‘complex’’ based on its architectural pattern and as ‘‘with’’ or ‘‘without’’ nuclear atypia. The presence of atypia significantly increases the risk of current presence or future occurrence of malignancy, whereas lesions without atypia are similar to exaggerated proliferative endometrium.[68] Lesions without atypia should regress with curettage or with progestin treatment and have little risk of progression to adenocarcinoma. In contrast, when atypia is present, the endometrium can be resistant to curettage or progestin treatment and can have significant risk of progression to adenocarcinoma.[68,69] Atypical lesions are ‘‘precancerous’’ and are distinguished from cancer by lack of stromal invasion.

Treatment of hyperplasia without atypia consists of cyclic progestin therapy similar to that used for anovulation (medroxyprogesterone acetate, 10 mg daily, for 10–14 days per month for 3 to 6 months) or even combined oral contraceptives.[69] Micronized progesterone (100–200 mg) in a vaginal cream is also an alternative when used from the tenth to the twenty-fifth day of the cycle for 3 to 6 months.[70] The use of the levonorgestrel IUD has been shown to be an effective treatment option.[71,72] For women who wish to conceive, ovulation induction is also an option for treatment.

Hyperplasia with atypia is best treated surgically with hysterectomy. If the diagnosis is made by endometrial biopsy, dilation and curettage should be performed to rule out concurrent adenocarcinoma, which may be present in 42% of these cases.[73] If the diagnosis is confirmed and no carcinoma is present, in women who strongly desire to retain their reproductive capability, high-dose progestins can be used, such as megestrol acetate, 40 to 80 mg daily, or medroxyprogesterone, 600 mg daily, for 3 to 6 months.[74,75] Resolution of atypical hyperplasia also has been seen after insertion of the levonorgestrel IUD.[77,81] Repeat biopsies need to be performed at 3-month intervals to confirm response to treatment and resolution. Most cases respond to medical treatments.[74,75] Women who respond to treatment should be encouraged to achieve pregnancy as soon as possible and, in the interim, be monitored closely because recurrence is not uncommon.[76] Women who delay childbearing should be maintained on progestin treatment and undergo sampling of the endometrium every 6 to 12 months. Women who do not respond to medical treatments should be treated with higher or longer doses of progestins or offered hysterectomy.

**Treatment of other causes of abnormal uterine bleeding**

When women experience abnormal bleeding for reasons other than those discussed previously, other conditions, such as chronic endometritis, should be considered. In chronic endometritis, endometrial biopsy demonstrates variable numbers of plasma cells within the endometrial stroma.[77]

Women may experience intermenstrual bleeding, spotting, postcoital bleeding, menorrhagia, or amenorrhea.[77] Endometritis may be caused by several processes, including infections, intrauterine foreign bodies or growths, and radiation therapy; however, a significant number of patients have no obvious cause. This condition is seldom the direct cause but may be a secondary or contributing cause of bleeding. Inflammatory cells in this condition produce proteolytic enzymes that delay normal healing and damage the endometrium, which makes it fragile and prone to erosions. These inflammatory cells also can release prostaglandins and platelet-activating factors, which are potent vasodilators. Chronic inflammation related to foreignbody reaction is the most likely cause for heavier bleeding associated with the copper IUD. Chronic endometritis may be one of the causes of abnormal bleeding in women with leiomyomas or polyps. The treatment consists of antibiotics, such as doxycycline, 100 mg, twice a day for 10–14 days.[78]

Fibroids are common, and in symptomatic women, abnormal uterine bleeding is the most common symptom. Because fibroids are common and most often asymptomatic, they cannot always be regarded as the cause of abnormal bleeding when they are found. Endovaginal ultrasound can help delineate fibroid size, location, and number, and sonohysterography demonstrates if there is impingement on the endometrial cavity. Fibroids that are submucosal or large enough to cause the overlying endometrium to stretch may cause friction, inflammation, or even ulceration, which lead to bleeding. Some myomas also have larger vessels on their surface, which can rupture and lead to heavy bleeding. Women with a grossly enlarged fibroid uterus, with multiple large fibroids distant to the endometrium, may have menorrhagia simply because of the larger surface area of the endometrium.

Intervention is initially medical, usually beginning with a combined estrogen- progestin treatment. Oral contraceptives decrease the volume and duration of blood loss during menses. NSAIDs and GnRHa also can help reduce menstrual blood volume and size of fibroids. Surgical management for fibroids is common, with technique determined by the size, location, and number of fibroids and patient age and future fertility desires.

Endometrial polyps result in abnormal uterine bleeding caused by the associated fragility of the endometrial vasculature, chronic inflammation, and surface erosions. Metrorrhagia is the most common bleeding pattern they cause; however, many polyps are asymptomatic.[79] Polyps are relatively easy to identify on sonohysterography; however, sometimes they can be detected on endometrial biopsy. When polyps are

identified, hysteroscopically guided removal is relatively straightforward and effective.[80]

Adenomyosis, the ectopic presence of endometrial glands and stroma within the myometrium, is a relatively common finding in women with menorrhagia and dysmenorrhea that is not caused by myomas or endometrial pathology. The pathogenesis is unknown; however, it is believed that the ectopic endometrial tissue seems to induce hypertrophy and hyperplasia of the surrounding myometrium, which results in a diffusely enlarged uterus. Adenomyosis can be suspected when myometrial cysts are seen on ultrasound or an increased junctional zone thickness on MRI.[81] Treatments include medical management with combined oral contraceptive pills, transdermal patch, vaginal ring, depot-medroxyprogesterone, GnRHa, or progestin IUD. Definitive therapy is hysterectomy, however.

**Bleeding disorders**

In women with unexplained menorrhagia, there is a substantial association with inherited coagulation defects, and screening coagulation studies are recommended.[82] Von Willebrand's disease is the most common inherited bleeding disorder in women with menorrhagia. In this disorder, there can be quantitative or qualitative derangements of the von Willebrand's factor, a protein necessary in platelet function and clot formation at sites of vascular injury. Von Willebrand's factor also serves as a carrier for factor VIII in the circulation. The disease has several different variations that result in disorders of differing severity of bleeding tendency between individuals.

The treatment is desmopressin, a synthetic analog of vasopressin, which is available in intravenous forms and nasal preparations.[83] Treatment leads to rapid increase in factor VIII and von Willebrand's factor and helps reduce bleeding. Of note, tranexamic acid also has been used successfully in this disorder, as have traditional treatments for menorrhagia, such as oral contraceptive pills.[83]

**MEDICATIONS DETAIL**

Estrogens, progestins, androgens, nonsteroidal anti-inflammatory drugs (NSAIDs), ergot derivatives, antifibrinolytics, and gonadotropin-releasing hormone (GnRH) agonists have been used to treat dysfunctional uterine bleeding (DUB). More recently, desmopressin has been used to control bleeding when associated with diagnosed bleeding disorders that do not respond entirely to traditional management.

Ergot derivatives are not recommended for treatment of DUB because they have been shown to be effective rarely in clinical studies and have many side effects.

At the onset of menses, secretory endometrium contains a high concentration of plasminogen activator. A reduction in menstrual blood loss has been demonstrated in some ovulatory patients taking ε-aminocaproic acid (EACA) or amino methyl cyclohexane-carboxylic acid (AMCHA) tranexamic acid, both potent antifibrinolytics. However, this therapeutic effect was no greater than that seen with oral contraceptive therapy. Antifibrinolytics are associated with significant side effects, such as severe nausea, diarrhea, headache, and allergic manifestations, and cannot be used in patients with renal failure. Because of the high side-effect profile and expense, these agents rarely are used today for this indication.

**Estrogens**

Very effective in controlling acute, profuse bleeding. Exerts a vasospastic action on capillary bleeding by affecting the level of fibrinogen, factor IV, and factor X in blood, as well as platelet aggregation and capillary permeability. Estrogen also induces formation of progesterone receptors, making subsequent treatment with progestins more effective.

Most DUB is secondary to anovulation. In these patients, endometrium continues to proliferate with asynchronous development. As blood supply is outgrown, irregular shedding occurs. Bleeding might be controlled acutely with high-dose estrogen for a short period of time. Several hours are required to induce mitotic activity, so most regimens require 48 h of therapy before continued bleeding is ruled a treatment failure.

Estrogen therapy only controls bleeding acutely and does not treat underlying cause. Appropriate long-term therapy can be administered once the acute episode has passed.

**Conjugated equine estrogen (Premarin):** Women in perimenopause generally are estrogen deficient and might experience bouts of estrogen withdrawal bleeding. Many of these patients will recover regular menses and develop an improved sense of well-being with the initiation of hormonal replacement therapy, including estrogen and a progestin.

**Progestins**

Occasional anovulatory bleeding that is not profuse or prolonged can be treated with progestins. Progestins inhibit estrogen receptor replenishment and activate 17-hydroxysteroid dehydrogenase in endometrial cells, converting estradiol to the less active estrone. Medroxyprogesterone acetate (Provera) is the most commonly used progestin in this country, but other types, including norethindrone acetate (Aygestin) and norethindrone (Micronor), are equally efficacious. In some patients in which systemic progestins are intolerable due to side effects, a progestin secreting IUD (Mirena) may be considered.

Synthetic progestins have an antimitotic effect, allowing the endometrium to become atrophic if administered continuously. These drugs are very effective in cases of

endometrial hyperplasia. In patients with chronic eugonadal anovulation who do not desire pregnancy, treatment with a progestin for 10-12 d/mo will allow for controlled, predictable menses and will protect the patient against the development of endometrial hyperplasia.

Some perimenopausal patients will not respond well to progestin therapy because of an inherent estrogen deficiency. Also, patients with thin, denuded endometrium occurring after several days of chronic bleeding might require induction of new endometrial proliferation by estrogen therapy first.

Avoid synthetic progestins in early pregnancy. They induce an endometrial response that is different from normal preimplantation secretory endometrium. Also, several reports suggest an association between intrauterine exposure to synthetic progestins in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5-8 per 1000 male births, might be doubled with early in-utero exposure to these drugs. Some synthetic progestins might cause virilization of female external genitalia in utero.

Patients at risk for conception can be treated safely with natural progesterone preparations. These preparations induce a normal secretory endometrium appropriate for implantation and subsequent growth of a developing conceptus.

**Medroxyprogesterone acetate (Provera):** Short-acting synthetic progestin. Drug of choice for patients with anovulatory DUB. After acute bleeding episode is controlled, can be used alone in patients with adequate amounts of endogenous estrogen to cause endometrial growth. Progestin therapy in adolescents produces regular cyclic withdrawal bleeding until positive feedback system matures.

Stops endometrial cell proliferation, allowing organized sloughing of cells after withdrawal. Typically does not stop acute bleeding episode but produces a normal bleeding episode following withdrawal.

**Combination oral contraceptives**

Contraceptive pills containing estrogen and progestin have been advocated for nonsmoking patients with DUB who desire contraception. Therapy also used to treat acute hemorrhagic uterine bleeding but is not as effective as regimens previously mentioned. Apparently takes longer to induce endometrial proliferation when progestin is present. In long-term management of DUB, combination oral contraceptives are very effective.

Ethinyl estradiol and a progestin derivative (examples: Ovral, Lo-Ovral, Ortho-Novum, Ovcon, Genora, Orthocyclen, and others): Reduces secretion of LH and FSH from pituitary by decreasing amount of GnRH.

**Androgens**

Certain androgenic preparations have been used historically to treat mild to moderate bleeding, particularly in ovulatory patients with abnormal uterine bleeding. These regimens offer no real advantage over other regimens and might cause irreversible signs of masculinization in the patient. They seldom are used for this indication today.

Use of androgens might stimulate erythropoiesis and clotting efficiency. Androgens alter endometrial tissue so that it becomes inactive and atrophic.

Danazol (Danocrine): Isoxazole derivative of 12 alpha-ethinyl testosterone.

**Nonsteroidal anti-inflammatory drugs**

Blocks formation of prostacyclin, an antagonist of thromboxane, which is a substance that accelerates platelet aggregation and initiates coagulation. Prostacyclin is produced in increased amounts in menorrhagic endometrium. Because NSAIDs inhibit blood prostacyclin formation, they might effectively decrease uterine blood flow. NSAIDs have been shown to treat menorrhagia in ovulatory cycles but generally are not effective for the management of DUB.

Naproxen (Anaprox, Naprelan, Naprosyn): Used for relief of mild to moderate pain. Inhibits inflammatory reactions and pain by decreasing activity of cyclo-oxygenase, which is responsible for prostaglandin synthesis.

**GnRH agonists**

Work by reducing concentration of GnRH receptors in the pituitary via receptor down regulation and induction of postreceptor effects, which suppress gonadotropin release. After an initial gonadotropin release associated with rising estradiol levels, gonadotropin levels fall to castrate levels, with resultant hypogonadism. This form of medical castration is very effective in inducing amenorrhea, thus breaking ongoing cycle of abnormal bleeding in many anovulatory patients. Because prolonged therapy with this form of medical castration is associated with osteoporosis and other postmenopausal side effects, its use is often limited in duration and add back therapy with a form of low-dose hormonal replacement is given. Because of the expense of these drugs, they usually are not used as a first line approach but can be used to achieve short-term relief from a bleeding problem, particularly in patients with renal failure or blood dyscrasia.

Depot leuprolide acetate (Lupron): Suppresses ovarian steroidogenesis by decreasing LH and FSH levels.

**Arginine vasopressin derivatives**

Indicated in patients with thromboembolic disorders.

Desmopressin acetate (DDAVP): Has been used to treat abnormal uterine bleeding in patients with coagulation defects. Transiently elevates factor VIII and von Willebrand factor.

**Surgical Care**
Most cases of DUB can be treated medically. Surgical measures are reserved for situations when medical therapy has failed or is contraindicated.

**Dilation and curettage**
D&C is an appropriate diagnostic step in a patient who fails to respond to hormonal management. The addition of hysteroscopy will aid in the treatment of endometrial polyps or the performance of directed uterine biopsies. As a rule, apply D&C rarely for therapeutic use in DUB because it has not been shown to be very efficacious.

**Hysterectomy**
Abdominal or vaginal hysterectomy might be necessary in patients who have failed or declined hormonal therapy, have symptomatic anemia, and who experience a disruption in their quality of life from persistent, unscheduled bleeding.

**Endometrial ablation**
Endometrial ablation is an alternative for those who wish to avoid hysterectomy or who are not candidates for major surgery. Ablation techniques are varied and can employ laser, rollerball, resectoscope, or thermal destructive modalities. Most of these procedures are associated with high patient satisfaction rates.

Pretreat the patient with an agent, such as leuprolide acetate, medroxyprogesterone acetate, or danazol, to thin the endometrium.

The ablation procedure is more conservative than hysterectomy and has a shorter recovery time. Some patients may have persistent bleeding and require repeat procedures or move on to hysterectomy. Rebleeding following ablation has raised concern about the possibility of an occult endometrial cancer developing within a pocket of active endometrium. Few reported cases exist, but further studies are needed to quantify this risk.

Endometrial ablation is not a form of contraception. Some studies report up to a 5% pregnancy rate in postablation procedures.

A study by Vitagliano *et al*. comparing thermal balloon ablation with transcervical endometrial resection in the treatment of DUB indicated that postoperative pain is greater following the thermal ablation procedure. In the study, 47 women with DUB underwent one of the two procedures, with pelvic pain evaluated one and four hours postoperatively and the need for analgesics assessed. Patients treated with thermal balloon ablation were found to have more pain at both evaluations, and the need for analgesic rescue dose was greater in this group. At 30-day postoperative evaluation, pain seemed to still be greater in these patients. However, complications such as heavy blood loss, uterine perforation, and thermal injuries did not occur in any of the study's patients.[84]

## OBJECTIVES, OPERATIONAL DEFINITIONS

### OBJECTIVES
The objective of the study was: "To determine the frequency of subclinical thyroid dysfunction among patients of menstrual irregularities."

### OPERATIONAL DEFINITIONS
**Dysfunctional Uterine Bleeding:** it can be cateeorized into oligornenorrhea, polymenorrhea, menorrhagia.
**Oligomenorrhea:** It's defined as infrequent menstruation where the duration between periods is more than 35 days.
**Polymenorrhea:** It's defined as frequent tnenstural bleeding where the duration between periods is less than 21 days.
**Menorrhagia:** Its defined as prolonged (greater than 7 days) and/or heavy (greater than 80m1) uterine bleeding occurring at regular intervals.
**Amenorrhea:** It's defined as absence of menstruation during reproductive years, it can be primary or secondary.

**Subclinical thyroid disorders**
It was measured as follows
Hormone - Reference value
TSH - 0.5-5.0 mIU/l
FREE T3 - 1.7-4.2 pg/mL
FREE T4 - 0.30-5.5 microlU/mL

## MATERIALS AND METHODS

### STUDY DESIGN
Cross Sectional Study.

### SETTING
Department of Obstetrics and Gynaecology, Unit II, Holy Family Hospital, Rawalpindi, Pakistan.

### DURATION OF STUDY
20th Jan 2022 to 19th July 2022.

### SAMPLE SIZE
Sample size is calculated by using WHO sample size calculator by taking confidence level =95% anticipated population proportion=33%[13] Margin of error=5% sample size (n)=340 cases.

### SAMPLE TECHNIQUE
Non-probability, consecutive sampling.

### SAMPLE SELECTION
**a. Inclusion Criteria**
- Age Group 18-45 years.
- With Menstrual Disturbance.

**b. Exclusion Criteria**

a. Presence of Palpable Pelvic Pathology.
b. Having known Thyroid Disorders
c. On Drugs like Aspirin, Heparin, Steroids, Amiodarone, Lithium.
d. Intrauterine contraceptive devices (IUCS) users.
e. With symptoms of thyroid dysfunctions.
f. On thyroid replacement therapy.

**DATA COLLECTION PROCEDURE**

This study was conducted at Department of Obstetrics and Gynaecology, Unit II, Holy Family, Rawalpindi. This study was conducted after approval from Hospital Ethics committee. Patient with confirmed diagnosis of dysfunctional uterine bleeding according to our operational definition and fulfilling the inclusion criteria of the study was registered for the study. A well-informed written consent was taken from all the patients or their care givers before enrolment. Clinical evaluation to diagnose dysfunctional uterine bleeding was done by the principal investigator of this study. Participants of the study were interviewed for menorrhagia oligomenorrhea, and amenorrhea. Detailed menstrual history and history associated with symptoms of Hypothyroidism and hyperthyroidism was taken. Participants were also clinically examined including GPE, Gentle abdominal, speculum and pervaginal examination. 5mg of venous blood was taken a plain glass tube without any anticoagulant. Morning sample in the fasting state was taken and serum was estimated for TSH, Free T3, Free T4.

**STATISTICAL ANALYSIS**

SPSS (v23) was used. Descriptive statistics were calculated for qualitative and quantitative variables. Quantitative variables including age and TSH levels were described using the mean ± standard. Qualitative variable like gender, TSH, bleeding pattern were measured as frequency and percentage.

Effect modifiers like age, bleeding pattern were controlled by stratification. Post stratification, chi-square test was applied. P-value < 0.05 was considered significant. Data was presented to tables and diagrams where appropriate.

**RESULTS**

Age range in this study was from 18 to 45 years with mean age of 28.06±4.70 years. Majority of the patients 254 (74.71%) were between 18 to 30 years of age as shown in Table I. Mean TSH levels were 4.49±2.21 mIU/l. Distribution of patients according to pattern of bleeding is shown in Table II.

Frequency of subclinical thyroid dysfunction among patients of menstrual irregularities was found in 95 (27.94%) patients as shown in Figure VI.

Stratification of polycystic ovarian syndrome with respect to age and bleeding pattern is shown in Table III & IV respectively.

**Table I: Age distribution of patients (n=340).**

| Age (in years) | No. of Patients | %age |
|---|---|---|
| 18-30 | 254 | 74.71 |
| 31-45 | 86 | 25.29 |
| Total | 340 | 100.0 |

**Mean ± SD = 28.06 ± 4.70 years**

**Table II: Distribution of patients according to pattern of bleeding (n=340).**

| Bleeding pattern | No. of Patients | %age |
|---|---|---|
| Oligomenorrhea | 158 | 46.47 |
| Polymenorrhea | 41 | 12.06 |
| Menorrhagia | 101 | 29.71 |
| Amenorrhea | 40 | 11.76 |

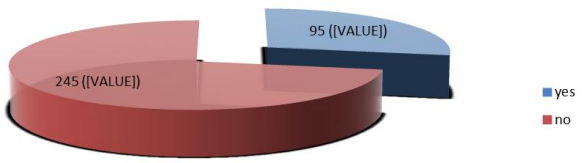


**Figure VI: Frequency of subclinical thyroid dysfunction among patients of menstrual irregularities (n=340).**

**Table III: Stratification of subclinical thyroid dysfunction with respect to age groups.**

| Age (years) | subclinical thyroid dysfunction | | p-value |
|---|---|---|---|
| | Yes | No | |
| 18-30 | 61 (24.02%) | 193 (75.98%) | 0.006 |
| 31-45 | 34 (39.53%) | 52 (60.47%) | |

**Table IV: Stratification of subclinical thyroid dysfunction with respect to bleeding pattern.**

| Bleeding pattern | subclinical thyroid dysfunction | | p-value |
|---|---|---|---|
| | Yes | No | |
| Oligomenorrhea | 41 (25.95%) | 117 (74.05%) | 0.0001 |
| Polymenorrhea | 17 (41.46%) | 24 (58.54%) | |
| Menorrhagia | 15 (14.85%) | 86 (85.15%) | |
| Amenorrhea | 22 (55.0%) | 18 (45.0%) | |

## DISCUSSION

Abnormal uterine bleeding is aberrant menstruation characterized by change 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 change in reproductive function including delayed onset of puberty, anovulatory cycles. Menorrhagia is the common manifestation of hypothyroidism. Majority of cases has subclinical hypothyroidism and pass unrecognized and is recognized as risk factor for menstrual problems, cardiovascular diseases and abnormal mental development in foetus.[85]

I have conducted this study to determine the frequency of subclinical thyroid dysfunction among patients of menstrual irregularities. Age range in this study was from 18 to 45 years with mean age of 28.06±4.70 years. Majority of the patients 254 (74.71%) were between 18 to 30 years of age. Frequency of subclinical thyroid dysfunction among patients of menstrual irregularities was found in 95 (27.94%) patients. According to study by Ali et al conducted in Pakistan recently, involving 234 patients of abnormal uterine bleeding and their thyroid status was also assessed which was showing the prevalence of subclinical thyroid dysfunction in 33% of the patients having AUB.[13]

In the study by Kaur[86], out of 100 patients studied, 14 had hypothyroidism. In the study by Sharma[87], prevalence of hypothyroidism was detected in 22% patients of DUB and hyperthyroidism in 14%. In the study by Pahwa[88], 22% cases of hypothyroidism and 76% of euthyroidism were reported, whereas Padmaleela[89] observed thyroid disorders in 26.5% patients of DUB. The prevalence of hyperthyroidism was 8.4% among the DUB patients as assessed by the findings of their thyroid function tests. Gowri[90] found 17.6% women with hypothyroidism, 2.7% with subclinical hypothyroidism, and 4.7% with hyperthyroidism.

Acharya *et al*. (2011) conducted a study on eighty patients of reproductive age, out of whom 46 (57.5%) had subclinical hypothyroidism and 34 (42.5%) had overt hypothyroidism. In subclinical hypothyroidism group the menstrual dysfunction which dominated was oligomenorrhea (28.2%) followed by menorrhagia (17.39%) and 39.13% had normal menstruation. They also concluded that subclinical hypothyroidism is one of the major etiological factors of infertility and it should be kept in mind while treating patients with infertility.[91]

Another study was conducted to determine the frequency of impaired thyroid function in patients with menstrual disturbances. 40 patients were taken: 82% of hypothyroidism and 18% of hyperthyroidism. 88% were married and 12% unmarried. However, the most common menstrual disturbance detected was menorrhagia (40%). Thus they concluded that thyroid dysfunction is associated with menstrual disturbances, so thyroid assessment should be performed in all patients with menstrual irregularities.[92]

Previous studies among women with menstrual disorders have reported thyroid dysfunction in varying rate among different population.[93,94] In a study among dysfunctional uterine bleeding patients, Sharma *et al*. reported hypothyroidism and hyperthyroidism in 22% and 14% patients respectively.[93] In study among 100 dysfunctional uterine bleeding patients by Pahwa *et al*. 22 were found to be hypothyroid, 2 hyperthyroid and the rest of the patients were euthyroid.[94] Previous studies among Nepalese population have also found thyroid dysfunction in large part of study population.[95,96]

The study done by Ajmani et al reported 20% as subclinical hypothyroidism, 14% as overt hypothyroidism, 2% subclinical hyperthyroidism and 8% overt hyperthyroidism and 56% as euthyroid.[97] Sangeeta et al reported in their study that 22% of cases were hypothyroid 2% hyperthyroid and 76% were euthyroid.[98] Pahwa *et al* study reported that their 72% of the hypothyroid patients had menorrhagia followed by Polymenorrhoea in 18%.[98] 64.3% cases of hypothyroid cases had menorrhagia followed by oligomenorrhoea in 21.4% cases in Kaur et al study.[99]

Joshi BR *et al*., reported 84.21% of patients as euthyroid and 15.79% patients with various thyroid dysfunctions, which is lowere to the present study.[100] In the study done by Wilansky DL and Greisman B, hypothyroid was seen in 22% of cases when compared to hypothyroid, incidence is lower.[101] Verma SK *et al*., observed 79.55% of patients as euthyroid, 19.5% of patients as hypothyroid and 1% of patients hyperthyroid.[102] So compared to these studies, hypothyroidism was noted in higher percentage of patients with AUB in present study.

Thyroid dysfunction has been found to be associated with menstrual disturbances, however there are findings showing both high and low frequency of menstrual

disorders in thyroid dysfunction.[103] Thyroid hormones affect menstrual cycle and both hyperthyroidism and hypothyroidism may result in menstrual disturbances.[104] Thyroid hormones play an important role in normal reproductive function both through direct effects on the ovaries and indirectly by interacting with sex hormone binding proteins. Thyroid dysfunction can lead to (reversible) menstrual irregularities and infertility. Treating thyroid dysfunction can reverse menstrual abnormalities and thus improve fertility.[105]

## CONCLUSION

This study concluded that the frequency of subclinical thyroid dysfunction among patients of menstrual irregularities is very high. So, we recommend that timely detection and management of thyroid disorder in patients presenting with menstrual disorders should be done in order to prevent unnecessary surgical interventions and morbidity of patients.

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