EVALUATION OF THYROID PROFILE IN PATIENTS WITH ABNORMAL UTERINE BLEEDING

Dissertation

Submitted to

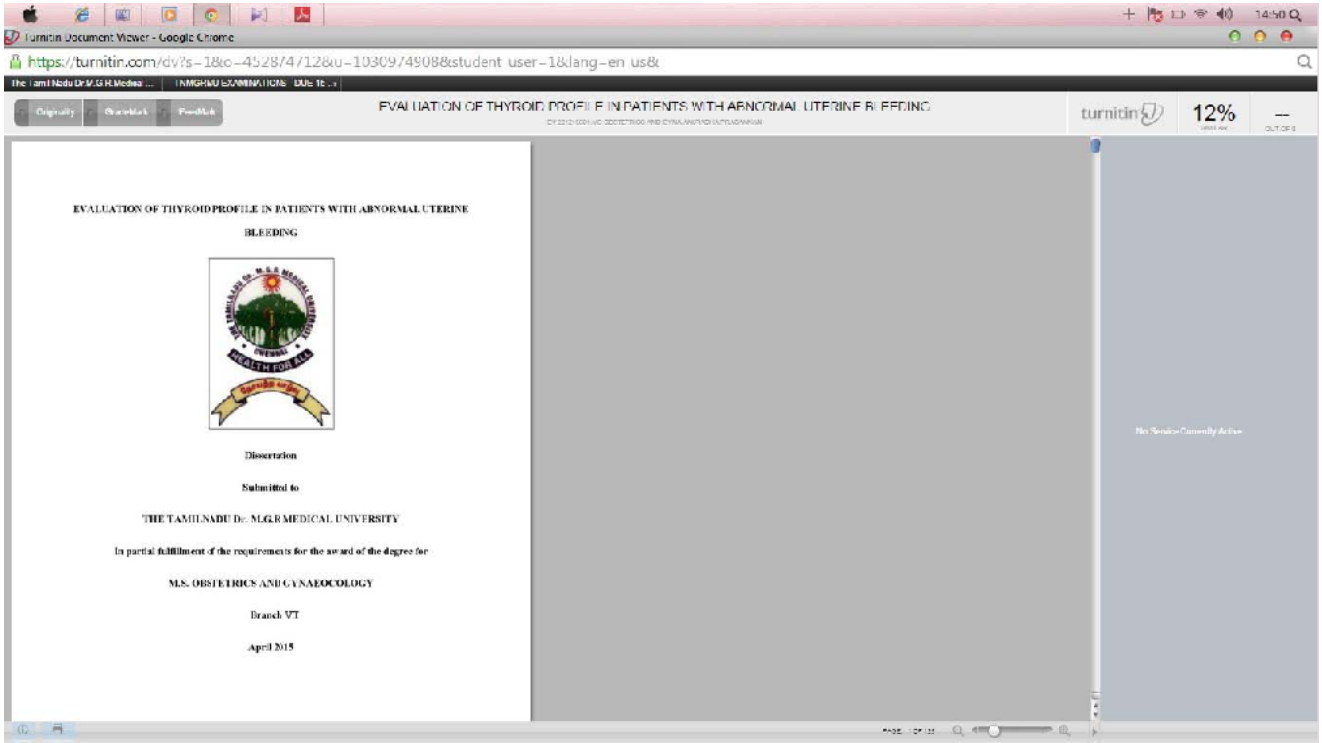
THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfillment of the requirements for the award of the degree of

M.S. OBSTETRICS AND GYNECOLOGY

Branch VI

April 2015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DECLARATION

I hereby declare that this dissertation entitled "**Evaluation of thyroid profile in patients with abnormal uterine bleeding"** is a bonafide and genuine research work carried out by me under the guidance of Dr. Usha Sadasivan, Professor, Department of Obstetrics and Gynecology, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamil Nadu.

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CERTIFICATE BY THE GUIDE

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ENDORSEMENT BY THE HOD AND HEAD OF THE INSTITUTION

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Dr. Anuradha Prasannan

CONTENTS

Introduction

1. INTRODUCTION

The word menstruation comes from the Greek word *menus* meaning both moon and power, and *men* meaning month. The blood from the womb was believed to nourish the unborn child and was considered 'mana' or 'breath of life.

One national study found that menstrual disorders were the reason for 19.1% of 20.1 million visits to physician office for gynecologic conditions over a two-year period. It has long been recognized that thyroid dysfunction may have profound effects on the female reproductive system. A relationship between the thyroid gland and the gonads is suggested by the common appearance of goiter during puberty, pregnancy and the menopause.[1] Thyroid disorders are insidious and ubiquitous in their presentation. Their role has been indicated in a wide spectrum of reproductive disorders ranging from abnormal sexual development to menstrual irregularities to infertility and premature menopause.[2]

In gynecology, 20% women present with abnormal uterine bleeding.[3] The underlying cause of DUB is still uncertain, but in most cases it is associated with failure of ovulation and is a consequent of hormonal imbalance. Ovarian dysfunction may be caused by either a primary defect or pathologic lesion within the ovary itself or it may be secondary to malfunction of other endocrine glands, notably the hypothalamus, pituitary and thyroid.[4]

Anovulatory or dysfunctional uterine bleeding includes the spectrum of abnormal menstrual bleeding patterns that occur in anovulatory women who

have no medical illness or pelvic pathology.[5] Abnormal uterine bleed includes both DUB and bleeding from structural causes. Anovulatory DUB is characterized by unpredictable irregular bleeding and ovulatory DUB is characterized by heavy and regular cycles or menorrhagia.[6] Fibroids, polyps, pregnancy complications, endometrial carcinoma etc include the structural causes. It can also be caused by contraceptive methods. Systemic causes include hypothyroidism, coagulation disorders and cirrhosis.[7] Bleeding due to a wide assortment of causes inside and outside the genital tract can masquerade as anovulatory bleed. Careful menstrual history and examination provides the information required to differentiate anovulation from other causes. When there is strong suspicion of pathology or treatment of presumed anovulatory bleed fails, additional evaluation is recommended.[5]

Menorrhagia is commonly tackled with hormonal therapy, curettage and hysterectomy with its attendant morbidity and mortality in many cases of anaemia, undiagnosed thyroid disease and coagulopathies.[8] Recently "occult" menorrhagia has been found to be an early manifestation of sub clinical hypothyroidism with the disease becoming symptomatic later.[9] The present study is to evaluate thyroid profile in patients with abnormal uterine bleeding.

Hypothesis & Justification

2. HYPOTHESIS AND JUSTIFICATION

There is a higher prevalence of hypothyroidism in patients with abnormal uterine bleeding. According to review of literature there is an association between thyroid profile and abnormal uterine bleeding. Therefore evaluation of thyroid profile will help in diagnosis of abnormal thyroid function in patients presenting with menstrual irregularities and help in treatment of the same. This study that explains the relation between thyroid profile and abnormal uterine bleeding can be used as a reference for further studies in future.[6]

Aims and Objectives

3. AIMS AND OBJECTIVES

i. To evaluate and compare the T_3, T_4 and TSH levels between patients with abnormal uterine bleeding and controls.

ii. To evaluate and compare the levels of thyroid profile in patients with abnormal uterine bleeding.

Review of Literature

4. REVIEW OF LITERATURE

- **Marinal Kanti Kundu. et. al.** selected 100 cases of DUB in their study. 23% had thyroid dysfunction, 13% subclinical hypothyroidism, 7% hypothyroidism and 3% hyperthyroidism. The study result found polymenorrhoea and menorrhagia as the most common forms of DUB.[10]
- **Talasila Sruthi et.al.** analysed 100 women presenting with menorrhagia, 11% had thyroid disorders, 8% had subclinical hypothyroidism, 2% hypothyroidism and 1% hyperthyroidism.[11]
- **Mangala Gowri B. et. al.** Found that in a study population of 170, 132 women had normal thyroid status, 30 had hypothyroidism & 5 had subclinical hypothyroidism. Eight women had hyperthyroidism.[12]
- **Carlo Saccardi. et. al.** Their study hypothesis was based on the double action of hypothyroidism and thyroxine intake, in subclinical TSH. Increased levels may be due to circadian oscillation that could stimulate the endometrial TSHRs.[13]
- **Anneli Stavreus Evers. et. al**. found that thyroid hormone is required for implantation, decreasing inflammation of endometrium & embryo development. Thyroid diseases often cause menstrual disturbance and infertility due to the lack of above actions.[14]
- **Anita Choudhary. et. al.** showed significant increase in platelet aggregability in the study population. Thyroid dysfunction can disturb the physiological process of hemostasis .[15]

- **Pushpa Sirichand. et. al.** study results found 82% of hypothyroidism, 18% hyperthyroidism .Here 88% were married and 12 % were single. Menorrhagia (40%) was the most common menstrual problem in the study population.[16]
- **Ajay Kumar. et. al.** observed decreased hemoglobin level in hypothyroidism patients. Administration of thyroxine increased hemoglobin levels which was statistically significant.[17]
- **Shivaleela M Biradar. et. al.** selected 100 subjects ,here 50 were women with primary infertlity and 50 healthy euthyroid fertile women. The study result showed increase in T3 and T4, decrease in TSH level in fertile women compared to the healthy women. 42% of the infertile women had thyroid dysfunction.[18]
- **Attia AH. et.al** studied forty euthyroid women with menorrhagia and 20 women with normal menstrual cycle. Statistically significant differences were observed in the thyroid profile on comparison of cases and controls.[19]
- **Jayakumar et.al** found that changes in the thyroid profile in relation to menstrual pattern were studied in congenital hypothyroidism. This study concluded that patients with anaemia and secondary menorrhagia were found to be associated with congenital hypothyroidism.[20]
- **Wilansky et. al** 67 patients were evaluated for functional status of the thyroid gland in yprimary hypothyroidism. Complaints of menorrhagia resolved in 3-6 months following administration of L-thyroxine in hypothyroid patients.[8]
- **Chakrabarti Jayita. et. al. S**tudied 50 women in reproductive age group with menorrhagia. The study results showed hypothyroidism in 20% of study population.[21]

- **Neelu Sharma. et. al.** In fifty patients with dysfunctional uterine bleeding (GP-A) in reproductive age group presenting with menstrual irregularities like menorrhagia, oligomenorrhoea, amenorrhoea, hypomenorrhoea and polymenorrhoea thyroid profile was evaluated and fifty thyroid patients in endocrinology were evaluated for menstrual patterns (GP-B). The study results showed hypothyroidism in 11 (22%) and hyperthyroidism in 7 (14%) women in (GP-A).In Group-B 56 % hypothyroid patients had disturbed menstrual cycles with associated problems and 62 % of hyperthyroid patients were found to have disturbed menstrual cycles ranging from menorrhagia to oligomenorrhoea to amenorrhoea.[22]
- **Tjinder Kaur et. al.** Studied 100 premenopausal women with DUB by evaluating their thyroid status and determining their serum TSH. 14 were hypothyroid, 1 hyperthyroid and remaining 85% were euthyroid. Out of the 14 hypothyroid women 9 (64.3%) had menorrhagia, 2 (14.3%) metrorrhagia and 3 (21.4%) had oligomenorrhoea, patient with hyperthyroidism were found to have hypomenorrhoea.[23]
- **Pahwa Sangeeta et. al**. Out of 100 cases, 22 were hypothyroid, 2 hyperthyroid and 76 euthyroid. 50% had menorrhagia and 75% metropathia haemorrhagica. 78.6 % of menorrhagia was seen in hypothyroid patients and 5.26 % in hyperthyroid patients.[24]

4.1. PHYSIOLOGY OF MENSTRUATION

Noyes, Hertig and Rock in 1950 described the cyclical histological changes in the endometrium.[25] Epithelial glandular cells, stromal-mesenchymal cells: and blood vessels of the endometrium cyclically replicate in reproductive-aged women. The superficial two thirds of the endometrium is the functionalis layer. It is composed of the deeply situated intermediate zone (stratum spongiosum) and a superficial compact zone (stratum compactum). It is shed and regenerated from the basalis layer about 400 times in a reproductive woman.[26]

4.1. a. Endometrial cycle

4.1. a. i. Proliferative phase

The first day of a cycle is the first day of menstrual bleed. The functionalis layer is fragmented and shed during menstruation and re-epithelialization is started. By fifth day epithelilization is completed and vascularization begins.[26] Initialy endometrium is thin about 2mm. Then the glands are narrow, tubular and are straight and parallel up to the surface. Mitotic figures are identified from day 5 and are seen in both epithelium and stroma up to day 16-17. The glands progress from a low columnar variety to a pseudostratified pattern before ovulation.[27] This is dependent on various estrogen regulated growth factors; epithelial growth by EGF and TGF-α, stromal growth by paracrine and autocrine action of estrogen and also fibroblast growth factor-9 and vessels get elongated under the influence of VEGF.[28,29] The glands then become widely spread

and stroma loose compared to the basal layer. The cells develop numerous microvilli that increase the surface area and cilia help in propulsion of endometrial secretion.[30]

4.1. a. ii. Secretory phase

Endometrial dating is a process of determining the day of menstrual cycle using histology. It is easier in the constant secretory phase than the variable proliferative phase. Now progesterone acts on an estrogen primed endometrium.

Day 17 endometrium shows accumulation of glycogen in the basal region of the glands, showing sub nuclear vacuoles and psuedostratification. This indicates ovulation has occurred.[31] Day 18: Vacuoles move to the apical region of the then, non ciliated cells.

Day 19: Cells begin to secrete glycoprotein and mucopolysaccharides into the lumen.[32] Mitosis ceases due to the antagonizing action of rising levels of progesterone. Type 2 17 β hydroxy steroid converts the estradiol present to inactive estrone.[33] Dating from mid to late secretory phase now depends on the structure of stroma. Day 21-24: Stroma becomes edematous.

Day 22-25: Stromal cells around the spiral arterioles begin to enlarge and stromal mitosis begins. The pre-decidual transformation of the functionalis layer heralds the window period for implantation. These changes are apt to receive a blastocyst. The glands develop extensive coiling and luminal secretions, the microvilli and cilia disappear and apical pinopodes appear. The surface glycocalyx undergoes changes.

Day 23-28: Shows predecidual cells surrounding the spiral arterioles. Day 24 is characterized by a pattern of decidual cuffing.

Changes in the vascularity are as follows spiral arterioles lengthen at an appreciably higher rate than the growth of endometrium this leads to more and more coiling of the already spiraling vessels. Perrot Applant demonstrated estrogen and progesterone receptors in smooth muscles of uterus and spiral arterioles. They mediate rapid angiogenesis through the production of VEGF by stromal and glandular epithelium.[34]

4.1. a. iii. Menstruation

If corpus luteum is rescued and progesterone production continues, decidualization continues, but if luteolysis is initiated, there will be cessation of glandular secretion and irregular breakdown of the functionalis layer. The sex steroids are withdrawn leading to profound vasospasm of spiral arterioles leading to endometrial ischemia a day or two before menses and stromal infiltration of inflammatory cells. The invading leukocytes secrete members of matrix metalloproteinases, which along with local proteolytic enzymes help in tissue breakdown. $PGF_{2\alpha}$ produced causes further arteriolar vasospasm, endometrial ischemia and myometrial contractions.[26]

4.1. b The ovarian cycle

4.1. b. i. Follicular phase

4.1. b. i. a) Primordial follicle

Primordial germs cells develop from the endoderm of yolk sac, hindgut and allantois of the embryo. They migrate to the genital ridge by 5-6 weeks. In fetal life the influence of HCG induces the proliferation of ovarian germ cells. It reaches a maximum number of 6-7 million by around 20 weeks of gestation. Only 2 million will be present at birth and only 3 hundred thousand at puberty. Only 400 will ovulate. Oogonia then enters meosis-I. A half million oogonia get arrested in the diplotene stage of prophase of meosis-I after birth. This step requires the action of ovarian determinant gene located on both arms of X-chromosomes and autosomes as well. A primordial follicle consists of this arrested oocyte and a single layer of granulosa cells. Follicles continue to grow and undergo atresia in all physiological circumstances.[35] This process is not interrupted by pregnancy or periods of anovulation and ovulation.

The mechanism determining the process of selection of follicles for a cycle is unknown. The follicle that has a timely match of readiness and tropic hormone stimulation may be the one destined for the lead role in a particular cycle. The early part of follicular growth is independent of any influence by gonadotrophins.[5] About three months before ovulation around 300 follicles are recruited for development. Out of these 30 become gonadotrophin dependent and start growing rapidly from the beginning of the

menstrual cycle.[36] If the follicles are not rescued by FSH they receed back to a process of atresia.

The molecular events that regulate the growth of the primordial follicle include a variety of locally produced and regulated factors. Growth of primordial follicle is upregulated by activin and down regulated by inhibin and their relative concentrations determine the size of the ovarian follicular pool in the fetus. AMH inhibits the growth of primordial follicle and bone morphogenic protein promotes growth. Neurotropic factors like NGF, BDNF, NT-3 and NT-4/5 also play a role. The oocyte is linked to the granulosa cells by gap junctions; they allow transport of ions, metabolites, cholesterol and C-AMP between granulosa cells and the developing oocyte. Gap junctions are formed by proteins known as connexins or GJA's. Expression of these proteins is upregulated by FSH and down regulated by LH. Gap junctions continue to act within the corpus luteum too.

As the corpus luteum from the previous cycle shuts down and all the luteal estrogen, progesterone and inhibin-A levels fall, FSH increases. FSH stimulates follicular growth and the cuboidal granulosa cells of the primordial follicle multiply to approximately 15 cells and it becomes the **PRIMARY FOLLICLE**. Granulosa cells are separated from the stroma by the basal lamina. Surrounding stromal cells also differentiate into concentric layers. When 3-6 layers of granulosa cells are formed, the stromal cells closer to the basal lamina differentiate into the theca interna and the outer portion into theca externa.[5]

4.1. b. i. b) Preantral follicle

The oocyte then enlarges and gets surrounded by a glycoprotein membrane known as the zona pellucida which separates it from the granulosa cells. Estrogens are produced by the action of aromatase enzyme complex. FSH binds to certain protein receptors on the preantral granulosa cells and induces aromatization. It helps in creating an estrogenic micro environment.[35]

4.1. b. i. c) Secondary follicles or the antral follicle

Under the influence of estrogen and FSH there is increased production of follicular fluid which accumulates in the intercellular spaces of the granulosa cells. They coalesce to form the fluid filled antrum. The granulosa cells surrounding the oocyte forms the cumlus oophorous. This fluid contains hormones, cytokines and growth factors that are necessary for the orderly maturation of the oocyte and the surrounding cells. In the presence of FSH, estrogen becomes the predominant component of antral fluid, the concentrations of which are much more than the circulating estrogen. In contrast an androgenic microenvironment antagonizes proliferation of granulosa cells and further leads to follicular atresia.[5, 35]

Two cell Two gonadotropin theory

The granulosa cells do not have several enzymes that play a role in the early part of steroidogenesis and therefore have to dependent on a supply of androgens. Androgens are produced as a result of stimulation by LH rather than FSH. At this stage it is the theca

cells and not the granulosa cells that have maximum number of LH receptors.[37] Therefore, LH stimulates theca cells to produce androgens, mainly androstenedione. This is then transported to the granulosa cells, where FSH stimulates the action of the aromatase enzyme complex and estrogen is produced. The estrogenic microenvironment thus created in the antral fluid is responsible for the growth and nutrition of the oocyte .[38]

The genes in the theca cells coding for LH receptors are, P_{450} scc and 3-β hydroxy steroid dehydrogenase. LH regulates the entry of LDL cholesterol into mitochondria for steroidogenesis. But the granulosa cells utilize HDL, in a different pathway only after lutenization. The theca cells express P_{450} c17 the rate limiting enzyme for synthesis of androgens. Granulosa cells do not have this enzyme. Thus granulosa cells are dependent on theca cells for their androgen supply. Theca cells express only P_{450}c17 and granulosa cells express only P_{450} arom (the aromatase enzyme). This confirms the "Two cell Two gonadotrophin theory".[5]

Both FSH and estrogen together have the following effects

i) Stimulate further estrogen production

ii) FSH receptor synthesis and expression

iii) Granulosa cell proliferation and differentiation.

Androgens have two positive feedback roles in the ovary, they are

i) Promoting proliferation of granulosa cells and enhancing aromatase activity.

ii) Inhibition of programmed cell death.[39]

The rising peripheral estrogen levels produce the following effects

a) Negative feedback on the hypothalamus and pituitary to decrease the production of FSH.[27]

b) It stimulates the production of inhibin-B which also inhibits the production of FSH.

The falling FSH level is a threat to continued follicular growth. Those follicles with the maximum number of FSH receptors bind most of the diminishing FSH. Thus, that follicle with the richest estrogenic microenviornment and the maximum FSH receptors (Follicle with maximum rate of granulosa cell proliferation) becomes the dominant follicle.[40]

There are other local autocrine and paracrine mechanisms acting in the selection of a dominant follicle.

a) The TNF produced by the granulosa cells inhibits FSH induced estradiol secretion everywhere except in the dominant follicle.

b) AMH suppresses the growth of lesser follicles, but not the dominant follicle.

c) By 9^{th} day vascularity from these theca cells becomes double fold and most of the secreted gonadotropins reach the dominant follicle in spite of a falling level of gonadotrophins.[5]

Four feedback mechanisms of gonadotrophin secretion

1. The long acting negative feedback mechanism:-The rising levels of estrogen produced by the graffian follicles, inhibits a further rise in FSH levels leading to inhibition of

other developing follicles. This action is mainly mediated by decreasing GnRH secretion in the hypothalamus. There may be a direct pituitary effect too, but to a lesser extent.

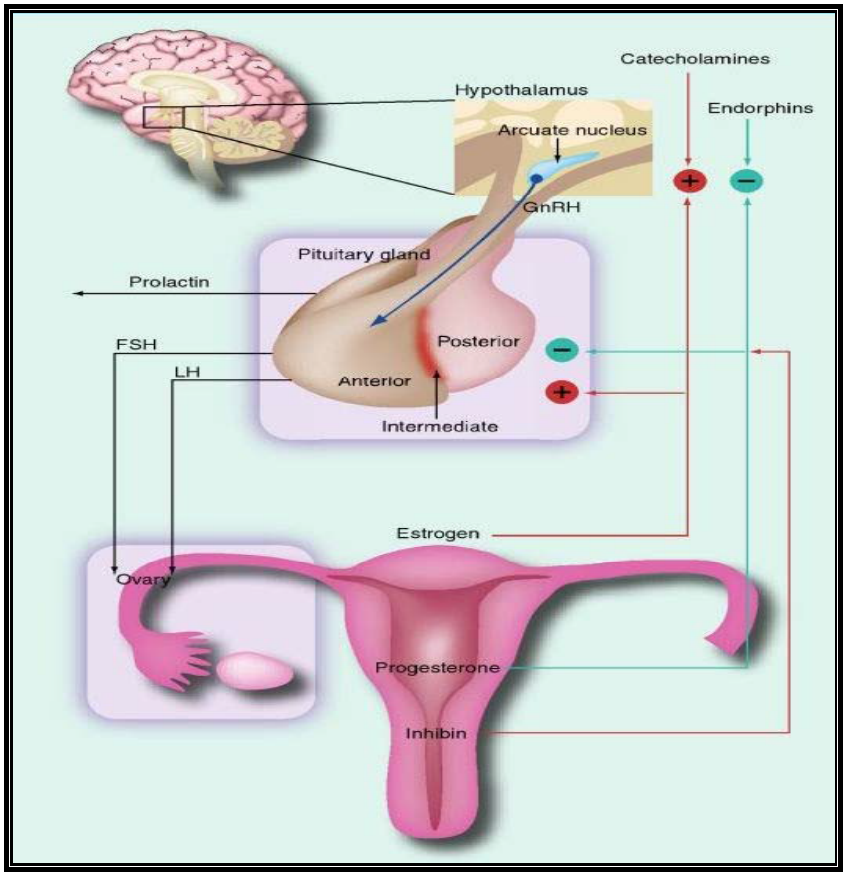
2. The long acting positive feedback mechanism-as estrogen levels rise, they eventually reach a sufficiently high level that stimulates the LH production and to a lesser extent the FSH production (The biphasic effect of estrogen - low levels of estrogen inhibits LH whereas at high levels it enhances LH secretion). This surge in hormone levels results in ovulation. This feedback mechanism, mainly acts at the pituitary level and to a lesser extent at the hypothalamus.

   Ovulation causes a temporary fall in the estrogen production, which shuts down the positive feedback effect but maintains the negative feedback effect therefore FSH and LH remains reduced until corpus luteum fails and estrogen and progesterone wanes. The hypothalamus, and to a lesser extent the pituitary are released from the inhibitory effect and FSH levels rise again in the new cycle.

3. The short acting feedback mechanism-the increasing secretion of FSH and LH by pituitary exerts negative feedback effect on the hypothalamic secretion of GnRH.

4. An ultra short acting feedback mechanism is also present which involves the self inhibition of hypothalamic regulating hormones as their levels rise.

Figure-1: Hypothalamo-pituitary ovarian axis



The positive feedback effect requires a sustained high level of estrogen about 200pg/ml for more than 48 hrs. This leads to an LH surge. Simultaneously the local FSH- estrogen interaction increases the number of LH receptors on granulosa cells. The peaking of LH hormone results in initiation of ovulation, production of progesterone and luteinisation of granulosa cells. This occurs 34-36 hours after initial rise of LH and 10-12 hrs after the surge.

There are other granulosa derived peptides playing a role in the pituitary feedback mechanisms. They are the inhibins and activins. The Inhibin-B acts in the follicular phase and Inhibin-A in the luteal phase. Both, inhibin A and B,inhibit FSH synthesis and release. Activin stimulates pituitary to release FSH and enhances its action on the ovary. Some other intra ovarian regulators that promote ovulation are Follistatin, IGF-1, EGF, FGF, TGF α and β, Interleukin 1, OMI and rennin-angiotensin.[27]

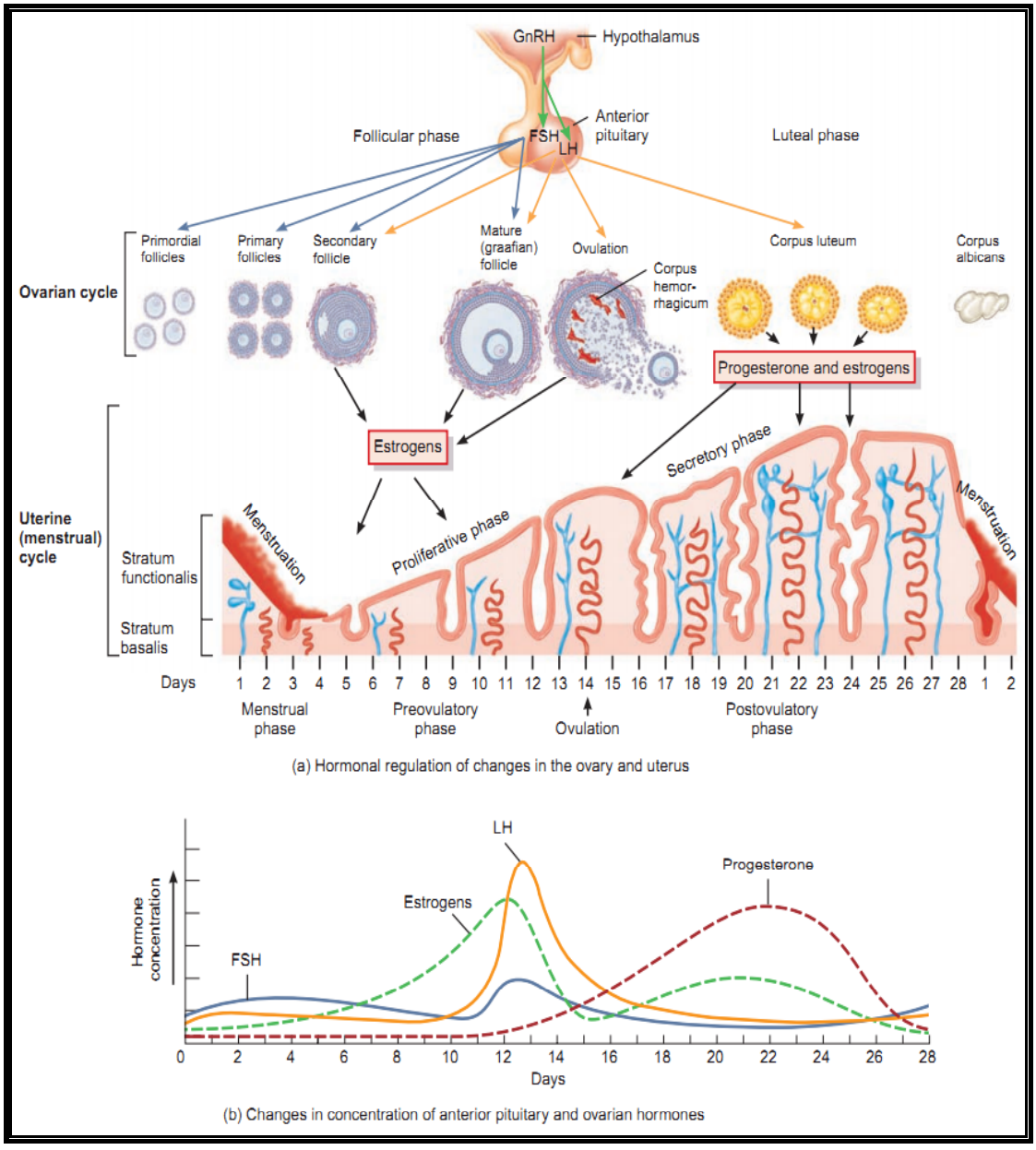
4.1. b. ii Ovulation

The arrested meosis restarts and the first polar body is extruded. The secondary oocyte immediately enters the second meiotic division and remains in metaphase until fertilization .The growing follicle reaches a size of about 2-3 cm in diameter; the dominant follicle forms a protrusion, the stigma, on the surface of ovary. The cell layers rupture and the ovum, surrounded by the corona radiata of granulosa cells, are released. The process takes place over a period of two mintues. The process is not an instantaneous rupture due to rise in intra follicular fluid level but a process of slow extrusion.[36] This is brought about by an increased distensibilty of the follicle wall and the prostaglandins synthesis by granulosa cells which causes the release of collagenases, lysosomes and plasminogen activator, leading to the erosion in the surface of ovary The main prostaglandin involved in ovulation is PGI2 (Prostocyclin).[35] The LH surge is responsible for prostaglandin production, early progesterone secretion, resumption of meosis and a decrease in the affinity of gonadotrophin receptors causing desensitisation to LH and also a transient decrease in estrogen leading to luteinisation.[36]

4. 1. b. iii. Luteal phase

Structure of corpus luteum-after ovulation the granulosa cells of the follicle take up lipids and a yellow luteal pigment gets deposited in them. These luteal cells produce progesterone. Here the basement membrane of the corpus luteum degenerates and proliferating blood vessels invade them. The luteal cells in addition to progesterone produce significant quantities of estrogen and Inhibin-A. The corpus luteal steroids estradiol and progesterone have a negative central feedback on the hypothalamus and pituitary which causes decrease in the FSH and LH secretion. The decreasing levels of Gonadotrophins s lead to no further follicular development. Inhibin-A secreted in luteal phase also inhibits FSH. Because of the falling levels of LH, the corpus luteal function diminishes progressively after 12-16 days and thus forms the scar like corpora albicans. The exact mechanism of luteolysis is not known. The regression of the corpus luteum leads to a fall in the sex steroids. This causes the withdrawal of the negative feedback effect on gonadotrophin secretion; FSH and LH begins to rise again and a new cohort is recruited.[27,41]

Figures-2: Physiology of menstruation



4.2. Normal menstrual bleeding

Among the different hormones acting on the endometrium, it is the action of estrogen and progesterone together that produces the most stable endometrium. Their combined withdrawal produces the most consistent menstrual characteristics. Most ovulatory women have a volume, pattern and duration of flow that they recognize as their own and are often accompanied by an equally consistent and predictable premenstrual molimina (breast tenderness, bloating and mood swings)

Variations in flow and cycle length are common at the extremes of reproductive age group. Cycles are often irregular during first 12-18 months after menarche due to immaturity of hypothalamo-pituitary ovarian axis. For the first 5-7 years after menarche cycles remain relatively long, then decreases gradually in length and becomes more regular.

In reproductive years, the overall cycle length and variability decreases and is lowest at 40-42 years. 8-10 years before menopause cycle length and variability increases and ovulation becomes irregular and infrequent. Variations in cycle length reflect the difference in length of the follicular phase. Few years after menarche, the luteal phase becomes extremely consistent about 13-15 days duration.

Most women have cycles that last from 24-35 days, but at least 20% of women experience irregular cycles. Usual duration of flow is 4-6 days, but approximately 3% have as less as 2 days and many upto7 days. Average volume of blood loss is 30 ml, greater than 80 ml being abnormal. Flow can be excessive without being abnormally

long, because most of the blood loss occurs in the first three days. Any deviation in the aforementioned patterns deserves evaluation.

4.2. a. Mechanisms involved in controlling onset and cessation of normal menstruation

Basically normal menstruation was described as the ischemic necrosis of the endometrium caused by vasoconstriction of spiral arterioles in the basal layer, due to withdrawal of steroid hormones. Towards the end of menstruation there would be longer and intense waves of vasoconstriction; along with coagulation due to vascular stasis, endometrial collapse and lastly rapid re-epithelialization by estrogen from the new follicles.

Recent perfusion studies do not support the classic hypoxia theory. Histology demonstrates the early endometrium as having focal necrosis, inflammation and coagulation, than a diffuse hyalinization or a coagulation necrosis that would be seen in hypoxia and vasoconstriction.

Now the central theme of the new model is, enzymatic autodigestion of the functional layer and the sub surface capillaries, possibly extending up to the spiral arterioles in the basal layer. The classical mechanisms towards the end of menstruation involving coagulation, local vasoconstriction and re-epithelialization are unchanged.

Enzymatic degradation involves the release of intracellular lysosomal enzymes, proteases from inflammatory cells and action of matrix metalloproteinases, all triggered by estrogen progesterone withdrawal. In the early secretory phase, acid phosphatase and other proteolytic enzymes within the intracellular lysosomes are inhibited by progesterone, through stabilization of lysosomal membranes. When hormone levels fall they destabilize, thus releasing the enzymes into the cytoplasm of the epithelial, stromal, and endothelial cells and their intercellular spaces digesting the surface membranes and intercellular bridges (desmosomes). In vascular endothelium it results in platelet deposition, prostaglandin release, thrombosis, extravasation of red blood cells and tissue necrosis. Endometrial cells have the capacity to synthesize certain chemokines (IL-8), which is kept inhibited by progesterone. When progestrone levels fall, the chemokines are released and leads to a recruitment of inflammatory cells. These cells also produce a wide variety of enzymes like matrix metalloproteinases (collagenases, gelatinases and stromolysins) that contribute to the process of degradation. Progesterone inhibits endometrial matrix metalloproteinases through the action of TGF-β. Progesterone withdrawal leads to its activation.

Progressive enzymatic degradation of endometrium leads to disruption of subsurface capillaries and venous system, which leads to interstitial hemorrhage and as surface membrane dissolves blood escapes into the uterine cavity. It also extends up to the deepest functional layer, leading to rupture of basal arterioles.

Menstrual fluid is comprised of endometrium rich in inflammatory infiltrate, red blood cells and proteolytic enzymes. Clotting of menstrual blood is prevented mainly by the action of plasmin, derived from its precursor plasminogen. The volume of menstrual blood loss is controlled by the balance between local- fibrinolytic and clotting mechanisms. Endometrial stromal cell tissue factor and plasminogen activator inhibitor (PAI-I) promote clotting. Early in menstruation intravascular platelet plugs and thrombi formation limits the blood loss. The cessation of menstrual bleed involves vasoconstriction of spiral arterioles, and also maybe of the radial arterioles in the superficial myometrium. The menstrual endometrium produces high concentrations of endothelins and prostaglandins, which cause intense vasoconstriction. $PGF_{2}\alpha$ is responsible for the myometrial contractions associated with this. Finally, surface re-epithelialization begining at the mouth of endometrial glands, spreading outward contributes to hemostasis. By the 5^{th} day these scattered areas of epithelial proliferation converge and fuse. The stroma regenerates from stem cells located in the basal layer of endometrium.

4.3. Pathophysiology of abnormal uterine bleeding

Anovulatory bleeding results from estrogen withdrawal accompanying the transient fall in estrogen caused by the regression of a follicular cohort. Otherwise it can be an estrogen break through bleed, from the focal breakthrough of an overgrown and fragile endometrium. Heaviest anovulatory bleed occurs in women with sustained elevated serum estrogen levels, women with PCOD, obese women,

post menarcheal girls and perimenopausal women. Ovarian hormone production and endometrial stimulation is unpredictable and disorganized in anovulatory bleeds. The anovulatory female is always in the follicular (proliferative phase) of endometrial cycle. As no ovulation has occurred, there is no luteal phase or secretory phase. Estrogen levels constantly fluctuate; rises and falls with the growth of each new cohort of follicles, but it ultimately loses its momentum and sooner or later lapses into atersia.

Uninterrupted estrogen growth stimulates the endometrium to proliferate to abnormal heights, but it becomes fragile. In the absence of the growth limiting and organizing effects of progesterone, there is an absence of the stromal support structure that provides stability. Few focal areas break down and bleed and later heal under the influence of continued estrogen production, followed by other areas. Persistent proliferative endometrium shows focal areas of stromal breakdown, pools of extravasated red blood cells, capillary platelet and fibrin thrombi and ball like aggregates of tightly packed stromal cells with a cap of hypertrophied epithelium. Venous capillaries are dilated and increased to form abnormal irregular channels, with abnormal ultra structural elements predisposing to fragility. Available evidence shows that, anovulatory bleeding results from an increased density of abnormal fragile vasculature, release of lysosomal proteolytic enzymes from epithelial, stromal and inflammatory cells. There is a local release of prostaglandins with more affinity for the vasodilatory PGE2 than the vasoconstrictor $PGF_{2\alpha}$. Molecules like perforins inhibit capillary plug formation and further degrade capillary network.

Vasoconstriction of the vessels of basal endometrium and superficial myometrium does not occur because tissue loss is only superficial, focal and does not reach the basal layer where denudation causes intense vasoconstriction. The final mechanism of epithelial reconstruction does not occur. The epithelial repair is only focal and it results in a constantly changing patchwork of small repairs, instead of organized well structured remodeling.[5]

4.4. Abnormal uterine bleeding

Abnormal uterine bleeding includes all abnormal menstrual patterns including spotting between periods, excessive bleeding during menstruation, prolonged duration of flow, menstrual cycles less than 21 days or more than 35 days and frequent cycles, as well as the absence of menstruation.

4.4. a. The types of abnormal menstrual patterns are

i. **Menorrhagia:** Menstrual cycles & menstruation occurring on a normal schedule, but with excessive flow and prolonged duration of flow >7 days.

ii. **Metrorrhagia:** Menstruation occurring at irregular intervals. The amount of blood loss & the number of days of vaginal bleed are not excessive in these patients.

iii. **Menometrorrhagia:** Characterized by irregular menstruation along with excessive bleed.

iv. **Polymenorrhea:** Menstrual cycle is less than 21 days long.

v. **Dysfunctional uterine bleeding:** Is a diagnosis given when there is no apparent cause for abnormal uterine bleeding. A diagnosis of DUB is made after excluding all other anatomic causes of abnormal uterine bleeding.

vi. **Oligomenorrhoea:** Menstrual cycles that occur more than 35 days apart.

vii. **Amenorrhoea:** Absence of menstruation.

a) **Primary amenorrhea:** when menstruation has not started by the age of 16 years.

b) **Secondary amenorrhea:** when menstruation has begun but has later ceased.

viii. **Intermenstrual uterine bleeding:** Vaginal bleeding (or) spotting that occurs between normal menstrual periods.[42, 43,44]

Due to the confusing nomenclature, lack of standardization of investigation and characterization of etiologies the proper management of abnormal uterine bleeding among non gravid women has been greatly affected. There may be a variety of potential causes coexisting in the same individual and on the contrary many entities that often could contribute to AUB, may be asymptomatic in the particular individual.[45]

Therefore the International Federation of Gynecology and Obstetrics (FIGO) has brought out a new classification system based on contributions from an international group of clinicians and investigators from 17 countries and 6 continents. There was a unanimous decision to discard the term "dysfunctional uterine bleeding".[46]

It was voted by a majority that the term "coagulopathy", "endometrial dysfunction" and "ovulatory disorders" should replace the term dysfunctional uterine

bleeding. So also, the term menorrhagia should be replaced by "heavy menstrual bleed".[47,48]

.4.4.b. Acute, chronic and intermenstrual AUB

In the meeting in Cape Town in 2009, chronic AUB was defined as bleeding from corpus that is abnormal in volume, timing and/ or regularity and is present for the major part of last six months. Acute AUB was defined as an episode of heavy bleeding that is of sufficient quantity to require immediate intervention to prevent further blood loss.[49] It can be superimposed on a chronic AUB or can occur without a prior history. Intermenstrual bleeding (IMD) occurs between clearly defined predictable and cyclical menses. It can occur randomly or may be predictable occurring at the same day in each cycle. This word would replace the term metrorrhagia.

There is a confusion regarding the exact meaning of the traditional terms, with different definitions followed by different authors in different countries. Sometimes the pattern of abnormal uterine bleed might not fall into any of the standard traditional terminologies and thus, will impair proper communication among health care providers.

Recommendations arising from an international consensus conference proposed terms to describe the most important features of menstrual bleeding during the reproductive years. Although the effort to simplify and standardize the terminologies of AUB is laudable a new nomenclature would take time to be accepted and adopted

by clinicians because however confusing the traditional terms are, they are firmly entrenched.[5]

Table-1: The proposed new terms by authors Fraser IS, Critchley HO and Munro MG[46]

Characteristics	Descriptive Terms	Normal Limits
Frequency on menses	Frequent	< 24 days
	Normal	24-38 Days
	Infrequent	> 38 days
Regularity (cycle to cycle - variation)	Absent	----
	Regular	+/- 2-20 days
	Irregular	> 20 days
Duration of flow	Prolonged	>8 days
	Normal	4-8 days
	Shortened	<4 days
Volume of monthly blood loss	Heavy	>80ml
	Normal	5-80ml
	Light	<5ml

4.4. c. The new proposed FIGO classification for abnormal uterine bleeding

There are 9 main categories arranged according to the acronym PALM-COEIN

The PALM group has structural entities that can be measured by imaging techniques or histopathology and the COEIN group has non structural entities that cannot be defined by either imaging or histopathology.

Table-2: PALM-COEIN classification of abnormal uterine bleeding

PALM		COEIN
Polyp		**C**oagulopathy
Adenomyosis		**O**vulatory dysfunction
Leiomyoma	**Submucosal**	**E**ndometrial
	Other	
Malignancy and hyperplasia		**I**atrogenic
		Not yet classified

The term DUB has been abandoned and not included in the system. The women, who would fall under this group, usually have one or more factors of coagulopathy, disorders of ovulation or a primary or secondary disturbance in local endometrial hemostasis. This system was formed taking into consideration the fact that, any patient would have one or more entities contributing to AUB and that sometimes definable entities like adenomyosis, polyps and myomas may be asymptomatic and do not contribute to the presenting symptoms at all.

Polyp (AUB - P)

This includes epithelial proliferation comprising of variable, glandular, vascular, fibromuscular and connective tissue component. They are usually benign. They are classified as being either present or absent, using one or a combination of imaging techniques with or without histopathology. Here polypoid appearing endometrium is excluded from this category.

Adenomyosis (AUB- A)

The prevalence of this condition is 5-7%. The diagnosis of adenomyosis is based on sonographic and MRI based diagnostic criteria. Sonographic appearance is based on the presence of heterotropic endometrial tissue in myometrium and is associated with myometrial hypertrophy.

Leiomyoma (AUB - L)

These are Benign fibromuscular tumors of myometrium, they are classified in the following manner:-

i) **Primary classification system:** The presence or absence of one or more leiomyomas irrespective of location and size based on a sonographic examination.

ii) **Secondary classification system**: Leimyoma involving endometrium, (SM) - submucosal is differentiated from others (O).

iii) **Tertiary classification system (ESHRE SYSTEM):** Based on the classification proposed by Wamsteker et.al.

Malignancy and hyperplasia (AUB - M)

They may be the cause of AUB or may be found in association with AUB and should be found in all women in the reproductive age group.

Coagulopathy (AUB - C)

Studies show that approximately 13 % women with heavy menstrual bleed have biochemically detectable disorders of hemostasis mostly Von Willebrand disease. It is not clearly defined as to how often they contribute to the genesis of AUB, or how often they are minimally symptomatic or asymptomatic. The heavy menstrual bleed associated with chronic anticoagulation is classified under this group

Ovulatory dysfunction (AUB-O)

This may present as a spectrum of abnormalities ranging from amenorrhoea, through infrequent and light bleeding to attacks of unpredictable extremely heavy menstrual bleed requiring intervention. These may be related to the absence of production of progesterone by corpus luteum in every cycle. And in later years is related to the disturbed ovulations. They are termed as "luteal out-of-phase" events.

Many of the ovulatory disorders may be due to endocrinopathies like PCOD, hypothyroidism, hyperprolactenemia, weight loss and obesity, mental stress or extreme exercise. It can be due to gonadal steroids or drugs affecting dopamine metabolism. It is frequently seen that the unexplained ovulatory disorders occurs at extremes of age - adolescence / perimenopausal.

Endometrial (AUB-E)

This occurs in cyclical menstrual bleed in the ovulatory cycles, when no other definable causes are identified and is due to a primary disorder of the endometrium. If the symptom is heavy menstrual bleed it may be due to an impairment of the local

endometrial hemostasis system. There may be deficiency in the production of local vasoconstrictors such as endothelin-1, $PGF_{2\alpha}$ or may be due to an excessive production of plasminogen activator (PA) leading to lysis of endometrial clot or increased production of vasodilators like PGE2 and prostacyclin.

It may also present as intermenstrual bleeding or prolonged bleeding. Prolonged bleeding may be due to a deficiency in molecular mechanisms of endometrial repair. It may be secondary to endometrial inflammation or infection, local inflammatory response or an aberration in endometrial vasculogenesis. There are data indicating an association between subclinical *chlamydial* infections with abnormal uterine bleeding. Diagnosis of endometrial disorders should be by a process of exclusion.

IATROGENIC (AUB-I)

This includes intrauterine devices and pharmacological agents that affects the endometrium, interferes with coagulation mechanism and influences the control of ovulation. Unscheduled endometrial bleed due to use of gonadal steroids is termed as break through bleeding. A single agent or combination gonadal steroid affect the hypothalamo-pituitary-ovarian axis and also has a direct effect on the endometrium. When continuous combination pills are given the patient has complete amenorrhoea. Here, any bleed is classified as breakthrough bleeding. This occurs because of a inadequate suppression of FSH with development of follicles that produce estradiol, irregular stimulation of the endometrium occurs leading to breakthrough bleeding. Other causes include intake of drugs that are hepatic enzyme (Cytochrome P450) inducers like

anticonvulsants and antibiotics, spotting caused by LNG-IUCD, drugs that inhibit dopamine metabolism and disturbing ovulation causing hyperprolactinemia,for example tricycle antidepressants and phenothiazines and last of all AUB is seen associated with the use of warfarin, heparin and low molecular weight heparin through impairment of vascular plug formation in the spiral arteries (but the this is to be included in the category AUB-C).

Not yet classified (AUB-N)

This group included many of the poorly defined conditions like- chronic endometritis, myometrial hyperplasia and arterio venous malformations. It also includes conditions in which further biochemical and molecular biological assays are required for a clear definition.

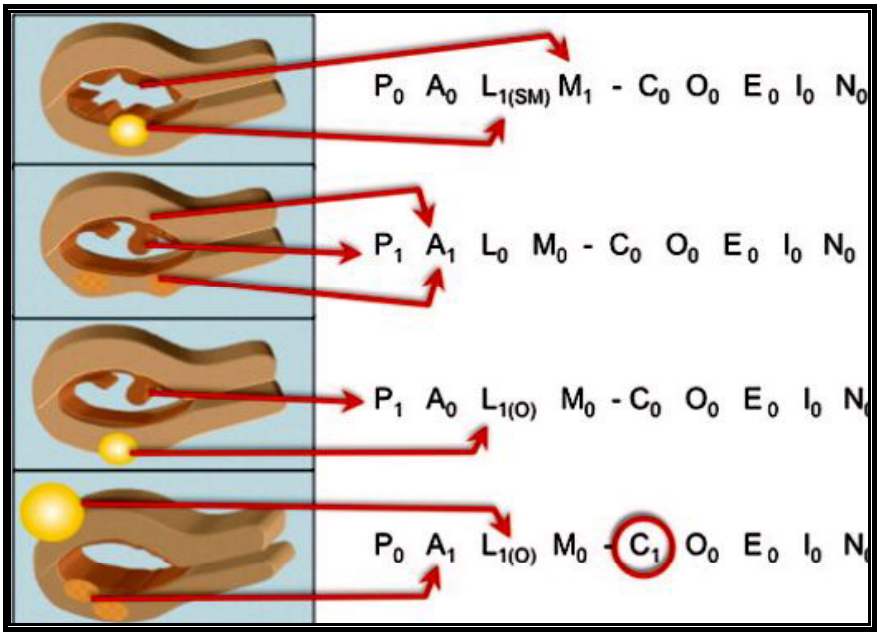
4.4. d. NOTATION

AUB may be caused by 1 or more causes in a particular individual. Therefore a system has to be developed to categorize and include all of it in the same individual. This simulates the TNM classification of tumors. The presence or absence of an entity in the PALM COEIN system is designated as "1" or "0"and not yet assessed as "?".

Eg. AUB P_0 A_0 $L_{1(SM)}$ M_0– C_0 O_1 E_0 I_0 N_0 - this patient has a disorder of ovulation and type 2 leiomyoma and no other abnormality.

AUB P_0 A_0 L_0 M_0 - C_0 O_0 E_1 I_0 N_0 - This patient has no abnormality other than endometrial causes.

Image-3: PALM COEIN Notation[50]



4.4. e. Guidelines for investigations

4.4. e .i. General assessment

A careful examination to ensure that the bleeding is not from a undiagnosed pregnancy and is from the cervical canal rather than from another location. Patient should be evaluated for anaemia with a hemoglobin or hematocrit. A full blood count including platelet count should be done. Then the clinician should proceed systematically and assess each component of the classification system.

4.4. e. ii. Determination of ovulatory status

Abnormal bleeding due to ovulatory disorders is associated with irregular timing and irregular flow and intermittent episodes of amenorrhoea. Further confirmation of ovulatory status can be done by measuring serum progesterone or a timed endometrial biopsy.[51]

4.4. e. iii. Screening for disorders of Hemostasis

Initial screening should be by a structured history. It has 90% sensitivity. Positive screen comprises of any one of the following

1. Heavy menstrual bleeding since menarche
2. One of the following
    a) Post partum hemorrhage
    b) Surgery related bleeding
    c) Bleeding due to dental procedures
3. Two or more of the following symptoms
    a) Bruising once or two times per month
    b) Epistaxis once or twice per month
    c) Frequent bleeding from gums
    d) Family history of similar bleeding symptoms

Patients with positive screen are further evaluated with assays for Von Willibrand factor, ristocetin and other assays. Patient is then referred to a hematologist.[52]

4.4. e. iv. Evaluation of endometrium

All patients with AUB do not require endometrial sampling. Patients are selected based on a combination of factors reflecting the risk of atypical hyperplasia or carcinoma. Factors like age, personal and genetic risk of carcinoma and transvaginal scan for endometrial thickness are taken into consideration.[53] Sampling is strongly recommended for women above 45 years.[54] Persistent unexplained / inadequately treated abnormal uterine bleed requires sampling, preferably along with hysteroscopic evaluation. It is also recommended to consider screening for *Chlamydia* in symptomatic patients.[55]

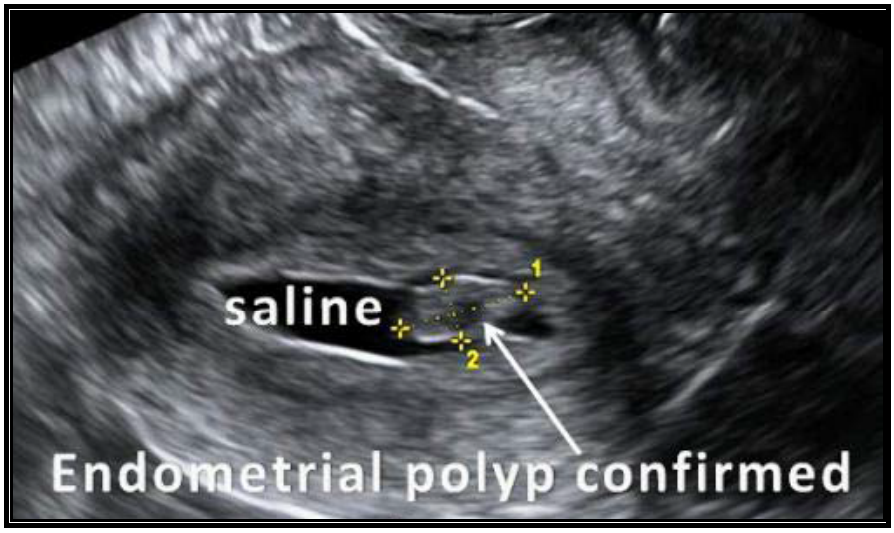
4.4. e. v. Evaluation of the structure of endometrial cavity

It should be done using a transvaginal ultrasound. To detect polyps and submucosal leiomyomas, ideally it should be the first screening tool. With good ultrasound images and with the absence of polyps or myomas the uterine cavity may be considered normal and as having no lesions contributing to AUB.

If imaging shows polyps or myomas encroaching endometrial cavity, or if the imaging is suboptimal, more sensitive imaging techniques are recommended. They are SIS-SALINE infusion sonography / hysterosonography / hysteroscopy.

In virgins, there is a role for MRI. With this the AUB – P or AUB – L_{SM} is diagnosed.

Image-4: Saline infusion Sonography



4.4. e. v. Evaluation of myometrium

A combination of transvaginal ultrasound and a transabdominal ultrasound is used to identify any leiomyomas and the AUB is classified as L_1. If this combination plus sis or hysteroscopy fails to identify any myoma then patient is categorized as L_0. If myoma is present a secondary classification is done using a combination of TVUS, SIS and M.R.I. Then a tertiary classification determining the relationship of leiomyoma with endometrium, myometrium and serosa is done.[50] Presence or absence of adenomyosis should be made out. MRI is a better investigation to clearly define these conditions, but in the present setting it is not practical to rely on it.[56]

4.4. f. Evaluation and management of AUB

4.4. f. i. Management of AUB in Adolescent age group

In adolescents AUB is due to the immaturity of hypothalamo pituitary ovarian axis. In the first few years after menarche FS, LH, estrogen and progesterone are all below the adult levels. They will have anovulatory cycles that will be manifested as irregular cycles. Bleeding disorders like Von Willebrand disease or thrombocytopenia or even leukemia's can manifest as menorrhagia or irregular bleed at menarche. These may constitute upto 20% of adolescent AUB.

A structured history regarding recent weight loss, eating and exercise habits and stress factors should be elicited. History of gum bleeding or a family history of bleeding disorder can suggest that the AUB is due to any of the generalized bleeding disorders. Examination should include B.M.I, features of virulization like hirsutism, acne, acanthosis nigrecans, petechiae, bruises and thyroid enlargement should be looked for. Local causes like foreign bodies, tumors like sarcoma botryoides or case of carcinoma vagina should be ruled out.

Investigation should include complete blood count, platelet, hemoglobin, and Von Willibrand panel including Vwf antigen assay, Factor VIII level and ristocetin cofactor assay. Thyroid function tests, pregnancy tests or imaging should be done as required.

Treatment

This depends on the degree of anemia and the amount of blood loss.

If there is no profound anemia or profuse blood loss then it can be treated by a combination of anti-fibrinolytic and anti-prostaglandin agents.

If bleeding is profuse and has produced severe anaemia, hormonal therapy is required. Adolescents have deficient endometrium therefore progesterone alone to treat the anovulatory cycle is not sufficient.

a) In cases where bleeding is very heavy they can be started on combined oral pills, four times daily and then tapered to once daily in a span of two-three weeks. It is followed by single daily dose, given cyclically for three to six months.

b) If hemaglobin is less than 8 gm/ dL, anemia should be corrected by blood transfusion.[57]

c) In acute heavy bleed, high dose estrogen may be required - conjugated equine Estrogen (25 mg) fourth hourly is given until bleeding is stopped.[58] Estrogen acts at the capillary level. After bleeding stops treatment can be continued as a 21 day course of combined oral pills and then stopped to give room for withdrawal bleed. But if the girl is anemic, a continued course without interruption for a period of 2-3 months will help in correcting the anaemia.

d) If bleeding is not profuse, conjugated equine estrogen at a lower dose of 1.25 mg fourth hourly is started and as bleeding stops it is tapered to single daily dosing for 7-10 days. After 10 days progestagens like medroxy progesterone

acetate 10 mg daily for next 10 days is given and then both together are withdrawn. This is followed by cyclical combined oral pill therapy.

a) Von Willebrand disease

Von Willebrand protein is a plasma protein which forms a complex with factor eight and prevents its proteolysis. It acts as a bridge between the damaged endothelium and the platelets. There are three types. Type 1 and 3 due to a quantitative defect and type 2 caused by qualitative defect. Desmopressin is the drug of choice in severe bleeding. If not controlled by desmopressin Vwf concentrate has to be administered.

b) Thrombocytopenia

This can be due to immune or non immune causes or as a part of bone marrow failure. Here correction of thrombocytopenia is required.

c) Thrombasthenia

If other tests are inconclusive tests for platelet functions should be carried out. Platelet function defects like glanzmanns disease and Bernard - Soulier disease can present as heavy menstrual bleed.

d) Other abnormalities of hemostasis

Dysfibrinogenemia, prothrombin deficiency, carriers of hemophilia who have decreased levels of factor VIII or IX, or deficiency of other clotting factors can present as menorrhagia. Treatment will include fresh frozen plasma or cryoprecipitate.

Adolescents with Polycystic ovarian syndrome can have oligomennorhoea or at times amenorrhoea followed by excessive bleed. Therefore cycles should be regularized. Medroxyprogesterone acetate can be given from day 1 to 10. In case any of the imaging studies demonstrate endometrial calcification in a patient with AUB, genital tuberculosis should be ruled out.[57]

4. 4. f. ii. Management of AUB in child bearing age group

When patients in this age group present, a detailed history including menstrual history, past history, family history and drug history is taken. A sudden change from normal to irregular menses may be pointing towards the diagnosis of pregnancy. Acute onset heavy menstrual bleed may be due to acquired defect in coagulation or points to a diagnosis of blood dyscracias. History of regular cycles with intermenstrual bleed suggests a fibroid polyp, submucus myoma or a premalignant or malignant lesion. The pattern of bleed in an anovulatory cycle is usually irregular without a definite pattern manifested as prolonged spotting per vagina or heavy menstrual bleeding without any pain. Ovulatory cycles have regular menses with mittelschmerz and premenstrual symptoms. History of passing clots rules out any coagulation defect.

A complete examination of the patient is done. The general condition assessed. History of gum bleed and easy bruisability is taken. Investigations should include a complete blood count including platelet and a peripheral smear. Thyroid function should be evaluated. ACOG bulletin recommends Von Willebrand panel assay in all patients with menorrhagia prior to hysterectomy. The endometrium of the patient is assessed by a

routine transvaginal ultrasound to see for any contributory anatomical lesions and any chance of malignancy should be ruled out (91-96% sensitivity). A thick endometrial shadow in a transvaginal scan can be a hyperplastic endometrium or a polyp. These are differentiated using a saline infusion hysterosonography (SIS). The third and the most accurate diagnostic tool is a hysteroscope. They can accurately differentiate between an anatomical lesion and a frank malignancy. An operative hysteroscopy allows a resection at the same sitting or a directed biopsy is taken. Alternatively endometrial sampling can be taken in the office setting using a PIPELLE aspirator or can be obtained by a conventional curettage that can be both diagnostic and therapeutic.[57]

Table-3: Types of endometrial hyperplasia with chances of malignancy[59]

Types of endometrial hyperplasia	Percentage (%)
Simple hyperplasia without atypia	1%
Simple hyperplasia with atypia	8%
Complex hyperplasia without atypia	3%
Complex hyperplasia with atypia.	29%

As per Fraser and Sengurtekein, excessive bleeding of uterine origin that is not due to a pelvic pathology or due to complications of pregnancy or any systemic disease is termed as dysfunctional uterine bleed. This can be both ovulatory and anovulatory.[60]

Management of anovulatory DUB in reproductive age group

It depends on the severity of the condition and the need for contraception. Patients should be counseled that irregular treatment can lead to even more erratic bleeding.

A) Progestagens: As the fundamental problem is an unopposed estrogen action and progesterone deficiency, progestagens can induce a medial curettage. 19-nor testosterone derivative, that is norethisterone is best for hemostasis. It can be started as 5 mg thrice daily, if bleeding persists escalate to 10mg thrice daily, it can be continued for as long as 15 days and then withdrawn. The next cycle should start with safer progesterone like medroxyprogesterone acetae. Treatment is continued for three such cycles. In case of an endometrial sampling report of complex hyperplasia, long term progestagens for nine months should be given.

B) In women desiring contraception combined estrogen progesterone pills and even transdermal patches can be used. Women desiring children can be treated with ovulation induction agent.

C) Levonorgestrel IUCD

This system delivers a 20 mcg of levonorgestrel to the uterus daily. Its effects are superior to oral contraceptive devices. 86% women experience a reduction in amount of flow within 3 months. Fertility is reversible with this treatment.[57]

Management of ovulatory DUB in reproductive age group

Here anti-fibrinolytic agents have a role. Patient can be treated with acombination of tranexamic acid and mefenamic acid. Combined oral pills can be used or a more

effective treatment would be the use of a Levonorgestrel IUCD. Other medical methods include Danazol which causes a suppression of gonadotropins, thereby ovulation and then inducing hypo or amenorrhoea. GnRH analogues as well as antagonists given in monthly high doses will suppress the pituitary.[57]

Minimally invasive surgeries for DUB

Endometrium is destroyed by means for different energy sources. Endometrial ablation has shown 90% reduction in bleeding and can cause even amennoerhoea.

They are of two types

A) First generation endometrial abalation: Resectoscopic endometrial ablation.

B) Second generation endometrial abalation: Non resectoscopic endometrial ablation.

A) First generation endometrial abalation

Resectoscopic endometrial ablation-it involves the use of the operative hysteroscope with the resectoscope. It was started in 1980's with basic concept borrowed from transurethral resection of prostate. Women with ovulatory DUB are the best candidates for this procedure. For those with AUB and bleeding disorders it serves as an adjuvant treatment. The rate of post procedure amenorrrhoea is 35%.Women having anovulatory bleeding benefit better with medical therapy with progestagens. Women with polycystic ovaries are not good candidates for endometrial ablation as there are chances for missing premalignant lesions of endometrium. Diagnostic hysteroscopy with

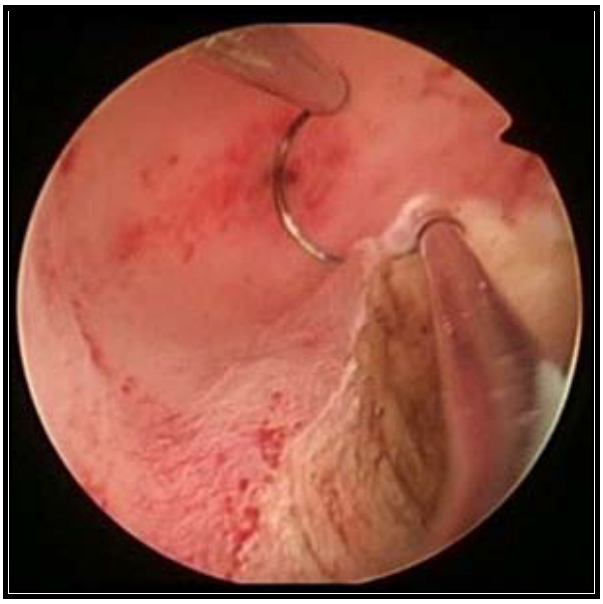
endometrial sampling is a must before this procedure. Women with submucous fibroids and polyp can also be treated by hysteroscopic resection.

Procedure

Distension media used are non-electrolyte distension media like sorbitol, glycine, dextran or mannitol. For the power source either eletrocautery or laser is used. The main instrument is a hysteroscope with a resectoscope.

The uterine cavity is distended with any of the above solutions. Then, with a wire loop electrode small strips of endometrium 7 mm wide and 4 mm deep are shaved off. This procedure is called Trans-cervical resection of endometrium (TCRE). There is a separate channel for the outflow of fluid and debris.[61]

Image-5: Trans-cervical resection of endometrium (TCRE)



Laser Ablation

Nd Yag laser is used for ablation of endometrium upto a depth of 6mm. Gold Rath. et. al. developed this technique in 1979. Success rates are about 83%, but the procedure is difficult to learn and is costly.

Roller ball ablation of endometrium

Ball electrode of 3mm connected to a monopolar coagulation system is used here. Roller ball is best for ablating the cornual regions. In presence of polyps and fibroids a combined procedure of resection and ablation is preferred. Pre-operative preparation with danazol helps in thinning the endometrium. This pre-operative preparation of endometrium showed higher rates of post-procedure amenorrhoea and lower rates of dysmenorrhoea along with shorter surgical time (Cochrane review).

Complications of endometrial ablation

1. **Distension media related complications:** This is commonly seen with non-electrolyte distension media as most of the solutions are hypo osmolar. If they get absorbed into the system it can cause dilutional hyponatremia, hypo osmolality and brain oedema. Premenopausal women, due to the inhibitory effect of oestogen and progesterone on the sodium pump are at a higher risk for brain oedema. The recent use of bipolar cautery facilitates the use of electrolyte medium like normal saline. There are automated systems available that help in measuring the fluid deficit in the system giving a clue about the intravasated fluid.

2. **Injury to viscera through a perforation in the uterus.**
3. **Long term complications like hematometra and pelvic pain.**
4. **Missing a diagnosis of endometrial carcinoma.**

30-40% of patients required a repeat procedure within 4 years.

B) Second generation

Non **R**esectoscopic **E**ndometrial **A**blation (NREA) without using a resectoscope, devices are kept inside the endometrial cavity and endometrium destroyed using different energy sources. These techniques have fewer complications; require shorter time and less training.

a) **Thermal balloon ablation:** A balloon is placed in the endometrial cavity and is distended using a pre-heated fluid. Two types of such devices.

   i. Therma choice system
   ii. Caveterm thermal balloon

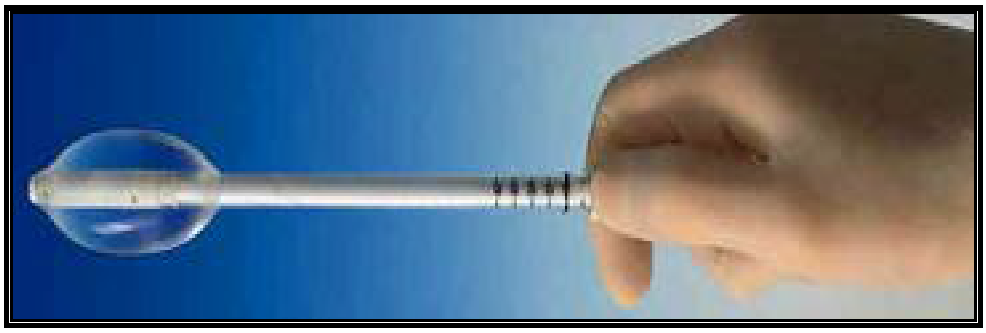
i. Therma choice system;

System consists of a disposable balloon catheter of 5.5 mm with a heating element inside. The pressure and temperature are set in the controller unit. The balloon is distended with 5% dextrose. The temperature is maintained at 87^0 C at 160-180 mmHg and treatment is given for 8 minutes. Complications like electrolyte imbalance and perforation are not present.

ii. Caveterm thermal balloon

The System consists of a flexible silicone balloon which approximate better with the endometrium. Glycine is pumped into the balloon at 75^0 C for a period of about 15 minutes.

Image-6: Caveterm thermal balloon



b) Microwave endometrial ablation: Endometrium is ablated using microwave energy at 9.2 GHz at 42 W. A depth of 5-6 mm can be obtained. Amenorrhoea rate is 53% and satisfaction rates are 87%. An important complication is perforation of uterus.

c) Cryotherapy Endometrium is destroyed by freezing to -90^0 C. A freeze zone of 1.5mm is obtained in 10 minutes.

d) Endometrial laser intrauterine thermo therapy (ELIT) : This device developed by Donez and Johns, consists of multiple laser fibers. Nd YAG laser or diode laser is used to obtain a depth of 6 mm in 5 minutes.

e) **Radiofrequency endometrial ablation:** The 1 year satisfaction rate with this technique was as high as 92.8%. No pre-operative thinning of uterine cavity is required. It can be done under local anesthesia. Here, radiofrequency energy is used for automated endometrial ablation. A 7.2 mm probe is used to deliver a bipolar current for 80-90 seconds. The depth of tissue is controlled automatically. The device available in market is Novasure.

f) **Thermal destruction with preheated fluid:** It is used in situations where the uterine cavity is distorted. Free fluid is instilled into the cavity at 90□C under a controlled pressure of < 40 cm of water for a period of 3 minutes, via a narrow disposable sheet of 3mm under hysteroscopic guidance.

g) **Photo dynamic therapy:** Endometrium is ablated by light of a particular wave-length with a photo sensitizer like 5-amino levulinic acid.[57]

Comparison of oral medical therapy, Levo norgestrol IUCD, EA and Hysterectomy

Only a minority of women were compliant with long term oral therapy. For women who refused medical treatment, who do not require fertility preservation, EA is an option. If fertility preservation is required levonorgestrol IUCD is preferred. The ablative procedures need theatre settings whereas IUCD insertion is an office procedure. The satisfaction rates were as high as 95% with hysterectomy compared to endometrial ablation. Therefore, hysterectomy was done in women who do not respond to conservative treatment and in those who had recurrence following minimally invasive surgeries.[62]

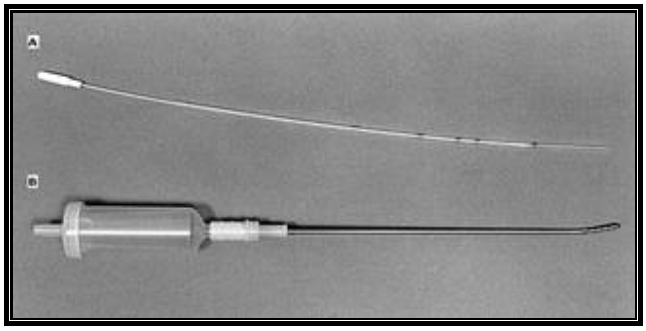
4.4. f. iii. Evaluation of AUB in perimenopausal age group

Here the most important aspect in the management of AUB is to rule out malignancy.

Patients developing AUB in this age group are thoroughly examined. Systemic and endocrine abnormalities are ruled out. Abdominal masses are looked out for. A complete gynecological examination is mandatory. A cervical smear including an endocervical smear with a brush is compulsory. The next important investigation is transvaginal ultrasound (TVUS) with careful evaluation of endometrium, myometrium, endocervix and adenxa. Focal and diffuse lesions are delineated by saline infusion sonography and finally a hystereoscopy.[57]

Endometrial sampling is mandatory in any woman with AUB in menopausal and perimenopausal age group. An endometrial thickness <4mm (9mm in tamoxifen users), absence of any irregularity and a normal sub endometrial halo is considered normal and sampling can be withheld. But if repeat bleeding occurs sampling must be done. For sampling, studies show that Pipelle aspirator is much superior to regular curettage and vacuum aspirator with a specimen adequacy of 84.1% for Pipelle than the lesser 45% for curettage with chances of missing focal lesions.[63] Hysteroscopy is the best way to diagnose benign as well as malignant focal lesions and a guided biopsy is most ideal.

Image-7: Pipelle aspirator



In case of polys and local lesions a hysteroscopic resection can be done in the same sitting. If histopathology reveals atypical hyperplasia hysterectomy is the treatment of choice. If malignancy is detected it must be treated accordingly. If no cause is found out bleeding may be anovulatory. Women with proliferative endometrium without atypia are treated with medroxyprogesterone acetate (10mg daily for 10 days a month or it can be given cyclically). Another option is the insertion of an LNG-IUCD. In women taking HRT (Hormone Replacement Therapy), irregular bleeding can be tackled by increasing the dose of progesterone. But if bleeding continues for more than 3-4 months, patients requires re-evaluation.[57]

4.5. Thyroid disease and female reproduction

4.5. a. Hypothyroidism

Hypothyroidism in women in the reproductive (20-40 years) is usually caused by Autoimmune Thyroid Disease (AITD). Hypothyroidism is associated with manifestations like abnormal sexual development, menstrual irregularities and infertility. The

association between hypothyroidism and abnormal menstrual patterns were recognized way back in the 1950s and changes in cycle length and blood flow were identified .The higher the serum TSH level more severe were the menstrual abnormalities. Severe hypothyroidism is associated with ovulatory dysfunction .This is caused by an associated hyperprolatcinaemia, caused by an increase in TRH production, and an alteration in GnRH pulsatile secretion. This leads to a delay in LH response and an inadequate corpus luteum.

The response of the ovaries to thyroid hormone could be explained by the presence of thyroid hormone receptors in human oocytes. The synergistic action of thyroid hormones on the FSH-mediated LH/HCG - receptor, helps to exerts a stimulatory effect on granulosa cell (for progesterone production). Hypothyroidism also causes an alteration in the peripheral metabolism of oestrogen and also decreases SHBG production. These mechanisms lead to an abnormal feedback effect at the pituitary level. Hypothyroidism can also alter the production of coagulation factors (decreased levels of factors VII, VIII, IX and XI) leading to menorrhagia.

4.5. b. Subclinical and overt hyperthyroidism

In hyperthyroid women, the production of SHBG is increased; the metabolism of estrogen altered, and there is an increased conversion of androgens to estrogen. Increased thyroid hormone levels, cause an increase in the gonadotropin response to GnRH and the baseline concentrations of gonadotropin is also elevated. The effect on hemostatic

factors, including the synthesis of factor VIII, explains the decreased menstrual flow. Treatment of hyperthyroidism frequently corrects the cycle changes.

4.5. c. Autoimmune thyroid disesase (AITD)

AITD is 5-10 times more prevalent in women than in men which may be due to various genetic factors, effects of estrogen and abnormalities in X chromosome. AITD is one of the commonest autoimmune disorders in women, affecting 5-10% of women in reproductive age group and also the most frequent cause of thyroid dysfunction.

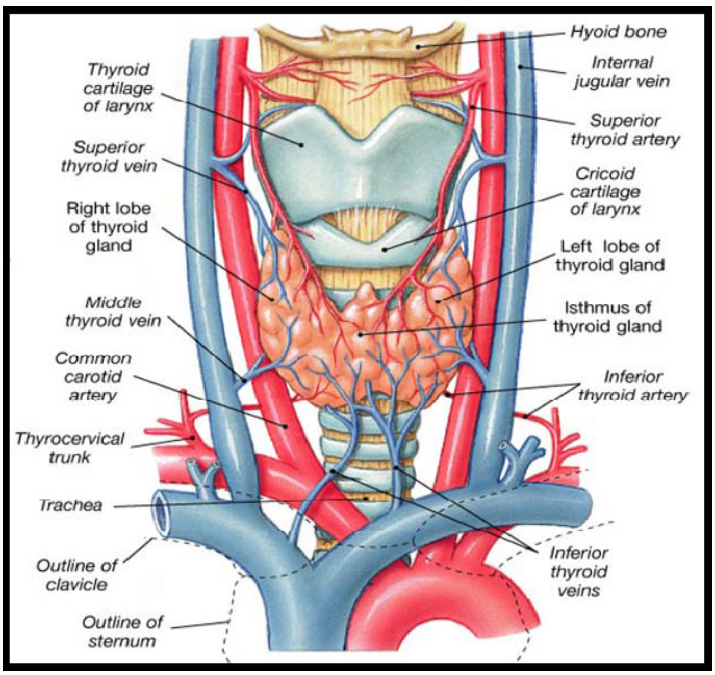
Adequate levels of thyroid hormones are quintessential in the normal steroidogenesis by ovary. T_3 modulates the effect of gonadotropins, FSH and LH on normal steroid biosynthesis. Studies have identified T_3 binding sites within human oocytes. Thyroid hormones potentiate the action of estrogen and enhance estrogenic responses, like prolactin production in the pituitary. This demonstrates the important role of thyroid hormones in normal reproductive function ; through their direct effects on the ovary and also indirectly by interacting with sex hormone binding globulins. Thus, abnormalities in thyroid hormone function can lead to reversible menstrual irregularities and infertility.[64, 65]

4.6. Endocrinology of thyroid gland

4.6. a. Historical perspective

First named by the anatomist THOMAS WHARTON in 1658 (meaning oblong shield), as the shape resembled the shields used in Ancient Greece. It was believed that the function of the thyroid was to fill vacant spaces and contribute to the shape and beauty of neck, especially in woman.[5]

Image-8-: Anatomy of the Thyroid gland



4.6. b. Chemistry of thyroid hormones

Iodination of amino acid tyrosine leads to formation of T_3 and T_4. One or more atoms added to tyrosine molecule; monoiodotyrosine (MIT) and diiodotyrosine (DIT) .[66]

$$DIT + DIT \rightarrow T_4 \text{ and } MIT + DIT \rightarrow T_3$$

4.6. c. Steps in synthesis of thyroid hormones

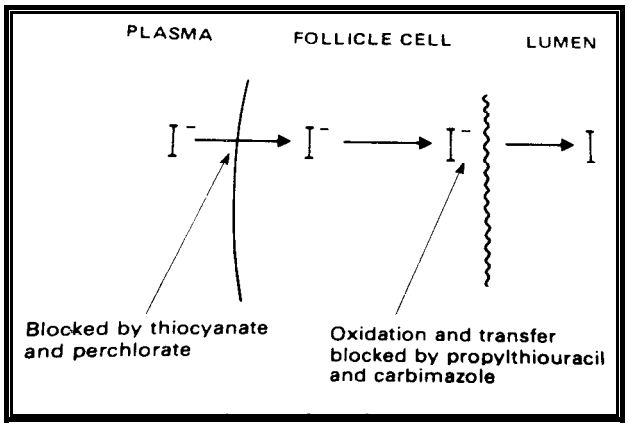
i) Iodine trapping:

Inorganic iodide gets absorbed and circulates in the blood (about 150 mcg) and is cleared by the thyroid. The thyroid to serum ratio of iodide is around 25:1 which rises to

250:1 in thyroid deficiency. Perchlorate and thiocyanate can block iodide pumps by competing with iodide for their carrier mechanism.

ii) Oxidation of iodide: The oxidation of iodide occurs at the cell colloid interface, in the microvilli with the help of membrane bound peroxidases. This process can be blocked by propylthiouracil and carbimazole.

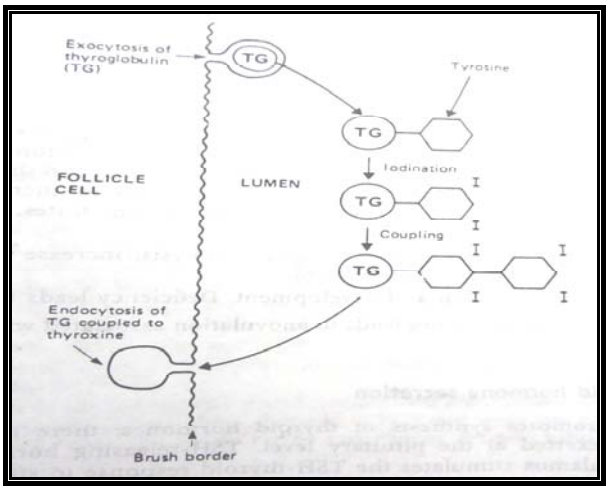
Image-9: Iodine trapping and oxidation



iii) Synthesis of thyroiglobulin: Thyroglobulin is synthesized in ribosomes and are then stored in vesicles. They are then extruded by exocytosis.

iv) Thyroid molecules attach to thyroglobulin molecules by peptide linkages within the lumen. Iodine then attaches to tyrosyl groups.

Image-10: Iodination of tyrosine and coupling



v) Coupling of iodotyrosines to form T_3 and T_4.MIT and DIT then undergo coupling to form triiodo and tetraiodo tyrosines, which remain attached to the thyroglobulin and forms the storage depot.

vi) Release of T_3 and T_4: Colloid is ingested by pinocytosis; then it undergoes proteolysis in lysosomes and releases T_3 and T_4 in ratio of 20-30:1.[67,68]

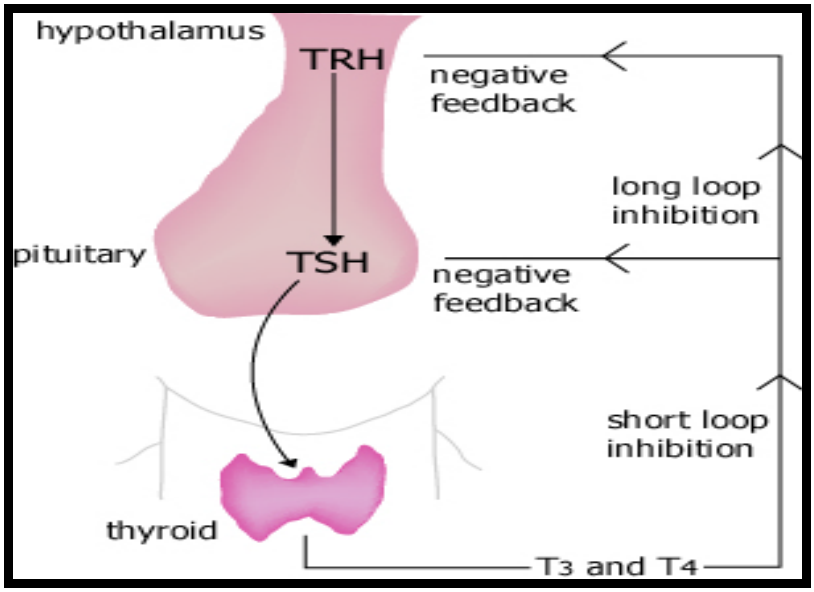
99.5% of thyroid hormone is protein bound. T_4 10 times more than T_3.75% of both hormones are bound to (TBG) thyroxine binding globulin; 15% of T_4 alone to thyroxine binding prealbumin and10 percent of T_4 and 25 percent of T_3 is bound to albumin. Free T_3 and T_4 are de-iodinated in cells all over the body.T_4 is converted toT_3 and free iodide which are excreted in the urine (20% in bile).A part of the T_4 is converted to the inactive isomer called reverse T_3.its levels increase in starvation, illness and after major surgery and in fetus from the conversion of the maternal T_4.[36]

The structure of Thyroxine was determined by Harrington and Barger in 1927, Tridothyronine by Gross, PittRivers and Roche et al in 1952.

4.6. d. Regulation of thyroid hormone

Neuroendocrine – hypothalamic pituitary – thyroid peripheral tissue axis regulates the thyroid hormone. Production of T3 and T4 in the thyroid gland is stimulated by the TSH (thyrotrophin, thyroid stimulating hormone) released from the thyrotrophs of anterior pituitary in response to hypothalamic TRH (thyrotrophin releasing hormone) .There is a negative feedback of thyroid hormones on the thyrotrophs such that when plasma concentrations of T3 and T4 are raised, TSH secretion is suppressed whereas cases with low T3 and T4 circulating TSH levels are high.[69]

Image-11: Hypothalamo Pituitary thyroid axis



4.6. e. Mechanism of action of thyroid hormones

Thyroid hormone receptors belong to a large family of nuclear receptors which include receptors for steroid hormones. The receptors function as hormone-activated transcription factors and modulate gene expression. Unlike steroid hormone receptors, thyroid hormone receptors bind DNA even in the absence of hormone, leading to transcriptional repression. Binding of hormone brings about a conformational change in the receptor, helping it to act a transcriptional factor.

Variation in expression of the different forms of thyroid hormone receptors in different tissues, in different stages of development

There are four different types of thyroid hormone receptors: alpha-1, alpha-2, beta-1 and beta-2.Of these alpha-1, alpha-2 and beta-1 isoforms are expressed in almost all tissues, whereas beta-2 is synthesized exclusively in hypothalamus, anterior pituitary and developing ear. The first receptor to be expressed in intrauterine life is α1 and beta receptors are increasingly expressed in the brain soon after birth. Beta receptors preferentially activates expression of genes important in brain development (e.g. myelin basic protein), and therefore upregulation of this particular receptor is crucial to the effects of thyroid hormones in the development of the fetal and neonatal brain. Thus, the presence of multiple forms of thyroid hormone receptors, with tissue and developmental stage-dependent difference in expression, suggests a high level of complexity in the physiologic effects of thyroid hormone.[70]

4.6. f. Physiological functions of thyroid hormones

a) **Carbohydrate Metabolism:** Increase the rate of hepatic glucose production, principally by increasing hepatic gluconeogenic activity.

b) **Protein Metabolism:** Stimulate the proteolysis mainly muscle.

c) **Lipid Metabolism:** Thyroid hormones increase lipolysis and also enhance lipogenesis

d) **Na-K Pump Activity:** Increases in the activity of the Na-K pump in the plasma membrane.

e) **Thermogenesis:** Increase the body temperature.

f) **Effect on BMR:** Increase the body BMR.

g) **Growth and development:** Normal human development.[71]

4.6. g. Thyroid during pregnancy

During pregnancy, the increasing levels of estrogen cause the TBG to increase upto three times. In most antenatal subjects, thyroid hormones levels remain fairly constant; whereas in some, the levels decrease by 10% approximately, though these individuals usually maintain euthyroid status. The resulting increase in thyroid hormone production, combined with increased levels of thyroid hormone metabolism (consequent loss of iodine in urine) and with fetal iodine uptake for its own thyroid hormone synthesis means that maternal iodine requirement increases slightly during pregnancy.[72]

4. 6.h. Thyroid Function Test

Determination of circulating levels of thyroid hormones is essential for an accurate assessment of the functional status of thyroid in patients. Serum thyroxine (T4) concentration was the most useful first line test for many years. Serum T4 is determined almost exclusively by RIA, values in euthyroid patient's ranges 5-12 µg/dl. In general (except T3 thyrotoxicosis etc.,) the value of T3 (serum triodothyronine) is parallel with T4 level and ranges in healthy subjects from 80-200 ng/dl. Reverse T3 (rT3) varies from 10-60 ng/dl. T3 values are often elevated in non-thyroidal illness. To assess the patients true metabolic status estimation of the concentration of free T4 or free T3 – the "active" hormones is advisable by equilibrium dialysis, which is the most precise method, although not available in all the centers.

Serum thyrotropin (thyroid stimulating hormone, TSH) has been a reliable indicator of primary hypothyroidism with levels rising even when thyroid deficiency is mild and T4 level still normal. Although RIAs were developed that could detect TSH concentrations in the range of 0.1-0.3 µg/ml, it was achieved only by extensive purification. Commercially available RIAs have not provided quantitative value s below 1 µU/ml. Second generation assays detect TSH in the range of 0.1 to 0.5 µU/ml and third generation assay have a 10 fold greater functional sensitivity.

Fourth generation assays are extremely sensitive and can detect TSH levels = 0.004 mU/l, but for practical purposes assay. Sensitive to = 0.1 mU/l are sufficient. The

widespread availability of TSH IRMA has made the TRH stimulation test virtually obsolute.[73]

4.6. i. Types of thyroid disorders

Specific kinds of thyroid disorders exist that include

- Hypothyroidism
- Hyperthyroidism
- Goiter
- Thyroid nodules
- Thyroid cancer

4.6. i. i. Hypothyroidism

It is caused due to the thyroid gland producing an insufficient amount of thyroid hormone. It can be due to problems within the thyroid gland, pituitary gland or hypothalamus.

Symptoms include: Fatigue, poor concentration or feeling mentally "foggy", constipation, feeling cold, fluid retention, muscle and joint aches, depression, prolonged or excessive menstrual bleeding in women.

Management of hypothyroidism

- **Levothyroxine (Synthetic Thyroxine / T4)**
- **Liothyronine (Synthetic Triiodothyronine / T3)**
- **Liotrix is a synthetic combination of thyroxine and triiodothyronine (T4 and T3)**.

4.6. i. ii. Hyperthyroidism

It is caused due to excessive production of thyroid hormone. It is less common condition than hypothyroidism. Symptoms relate to increased metabolism in cases of hyperthyroidism. Apparent symptoms may not be present in mild cases.

Symptoms and signs: Tremor, nervousness, increased heart rate, fatigue, intolerance for heat, increase in bowel movements, increased sweating, concentration problems and unintentional weight loss.

Management of hyperthyroidism

Classification of Anti-thyroid drugs

Class-I: Inhibit Hormone synthesis (Anti-thyroid drugs): Propylthiouracil, Methimazole, Carbimazole.

Class-II: Inhibit iodide trapping: Thio-cyanates, Perchlorates, Nitrates.

Class-III: Inhibit hormone release: Iodine, Sodium Iodide, Potassium Iodide, Organic Iodide.

Class-IV: Destroy thyroid tissue: ^{131}I, ^{125}I and ^{123}I.[74, 75]

Thyroidectomy: Subtotal thyroidectomy is the oldest form of treatment for hyperthyroidism. Others include total thyroidectomy, combinations of hemithyroidectomies, contralateral & subtotal thyroidectomies.

4.6. j. Diagnosis of thyroid disorders

General Survey

1. Build and nutrition – Patients suffering from thyrotoxicosis are usually thin and underweight. They have excessive sweating, moist skin & muscle wasting. In hypothyroidism reverse is true (dry skin, obese).
2. Facies – In patients suffering from thyrotoxicosis there is a facial expression of excitement, tension, nervousness with or without variable degree of exopthalmus. Mask like puffy face is seen in hypothyroidism.
3. Mental State and intelligence - Hypothyroid patients are dull with low intelligence level.
4. Pulse rate - Sleeping pulse rate is very useful index to determine the degree of thyrotoxicosis.

5. Eye signs should be looked for in primary thyrotoxicosis.

- Lid retraction: Upper eye lid is higher than normal
- Exopthalmos: Eyeball is pushed forwards due to increase in fat / odema / cellular infiltration in the retroorbital space
- Eyelids are retracted: Weakness of ocular muscles (Opthalmoplegia) by examining eye movements.
- Chemosis (oedema) of conjunctiva are eye signs to be looked for.

6. Thyroid is examined for any enlargement, nodules cyst or any features suggestive of Malignancy.

7. Blood test: To measure levels of thyroid hormones T3, T4, TSH. Other tests may include Antibodies against thyroid tissue e.g. anti-thyroglobulin, anti-thyroperoxidase or TSH receptor stimulating antibodies.

8. Ultrasound: Helps in visualization of the consistency of the tissue within the gland. Cysts / calcifications / increased vascularity may be revealed.

9. Thyroid scans using radioactive iodine: Intravenous administration of radioactively labeled iodine results in uptake by the thyroid gland which is visualized by imaging test. Areas or nodules producing excess hormone (hyperfunctioning) shows an increased uptake of iodine.

10. Fine needle aspiration and biopsy: include techniques that remove a sample of cells or tissue from the thyroid gland for examination and diagnosis by a pathologist.[76]

Materials and Methods

5. Materials and Methods

5.1. Study design: It is a cross sectional study.

5.2. Study setting: The study was conducted in Department of Obstetrics and Gynecology in Sree Mookambika Institute of Medical Sciences Hospital, Kulasekharam.

5.3. Duration of stud: Study was conducted in the period of 2013-2014 year.

5.4. Sample size calculation

Sample size is selected by Epi info software. Power 80, confidence interval 95%, prevalence of control 1% and case are 23.4% and the calculated sample was 30 in cases and 30 in control.

Formula for sample size= $4pq/d^2$

Where

P= The prevalence

q= (100-p)

d=allowed error (5-20% of p)

5.5. Study groups

Group-I: (Control) – Randomly selected patients in the age group of 15-45.Patients without any menstrual complaints. (Every first patient presenting to the Gynecology

O.P.D. on the Mondays of first three weeks in a month with complains other than menstrual abnormalities will be selected)

Group-II: (Cases) - Patients with abnormal uterine bleeding (Any case presenting to the Gynecology O.P.D. with complains of menstrual abnormalities in the same age group)

5.6. Inclusion criteria

- Women between 15-45 years of age,
- Patients presenting with abnormal uterine bleeding.

5.7. Exclusion criteria

- Patients with thyroid tumor.
- Women on anti-thyroid medication.
- Patients with recent thyroid surgeries.
- Endometrial, uterine and any other reproductive organ cancers.
- Organic lesions of genital tract.
- Bleeding disorders.
- IUCD users.
- Pregnancy complication.[77]

5.8. Observation

5.8. a. Demographic data

Case and control group's patient's demographic data (age, occupation, Material status, socioeconomic status) was collected by interview. Past and family history also collected from all the study population.

5.8. b. Chief complaints

Patients came to the OPD Gynecology department was asked for the chief compliments (bleeding per vagina) and other any complaints recorded in the case sheet.

5.8. c. Gynecological history

All the patients menstrual history, details previous menstrual cycle, obstetric history was collected.

5.8. d. Clinical examination

All the patients were subjected for general and clinical examination. Blood pressure, pulse rate, systemic examination and gynecological examination including per abdomen, vulvo vaginal examination (Healthy/Non Healthy), per speculum examination and bimanual Vaginal Examination. Ultrasound was also performed in all the patients.[78]

5.8.e. Biochemical investigations

From controls and cases 2 ml of blood was collected and used to measure Hb (Sahli Method), platelet count (Auto mated platelet counter), Bleeding time (Duke Method), clotting time (Capillary tube method). Serum was separated and used for the estimation of thyroid hormones by ELISA method.

5. 8. f. Thyroid hormone (T_3, T_4, &TSH) estimation by ELISA method

5.8. f. i. Specimen collection and preparation: Serum prepared from a whole blood specimen obtained by acceptable medical techniques. Serum sample stored at 48 hours at 2-8°C prior to assaying.

5.8. f. ii. Instruments and materials: A micro titer well reader with a bandwidth of 10nm or less and an optical density range of 0 to 2 OD or greater at 450 nm wavelength is acceptable for absorbance measurement. Distilled water, micropipettes (0.5, 1, 2 and 5 ml), pipette tips, absorbent materials and ELISA reader are required

5.8. f. iii. Assay Procedure

1. Secure the desired number of coated wells in the holder

2. Dispense 100 µl of standards, specimens, and controls (not included in kit) into appropriate wells.

3. Dispense 100 µl of Enzyme Conjugate Reagent into each well.

4. Thoroughly mix for 30 seconds. It is very important to have completed mixing.

5. Incubate at room temperature (18-25°C) with shaking at 175±25 RPM for 120 minutes (2 hours).

6. Remove the incubation mixture by flicking plate contents into a waste container.

7. Rinse and flick the microtiter wells 5 times with distilled or dionized water. (Please do not use tap water.)

8. Strike the wells sharply onto absorbent paper or paper towels to remove all residual water droplets.

9. Dispense 100 µl of TMB Reagent into each well. Gently mix for 5 seconds.

10. Incubate at room temperature, for 20 minutes.

11. Stop the reaction by adding 100 µl of Stop Solution into each well.

12. Gently mix for 30 seconds. Ensure that all of the blue color, changes completely to yellow.

13. Read OD at 450 nm with a microtiter well reader within 15minutes.[79]

Hormone	**T_3**	**T_4**	**TSH**
Normal lab values	2.15-6.45 p mol/L	10.32 -25.8 p mol/L	0.39 -6.16 p mol/L

5.8.12. Statistical analysis

The data was analyzed by SPSS (16.0) version. Chi-square and t- test was applied to find the statistical significance at 95% confidence interval between group-I and II. The p value less than 0.05 will be considered statistically significant. Data was expressed in number, percentage and MEAN±SEM.[80]

Results

6. Results

6.1. Assessment of demographic data

Table-4: Distribution of number of patients according to age in cases and controls groups

Age (years)	Group-I (Control)	Group-II (Cases)
<20 years	00	02
21-30 years	07	05
31-40 years	14	10
41-45 years	09	13

Graph-12: Distribution of percentage of patients according to age in cases and controls groups

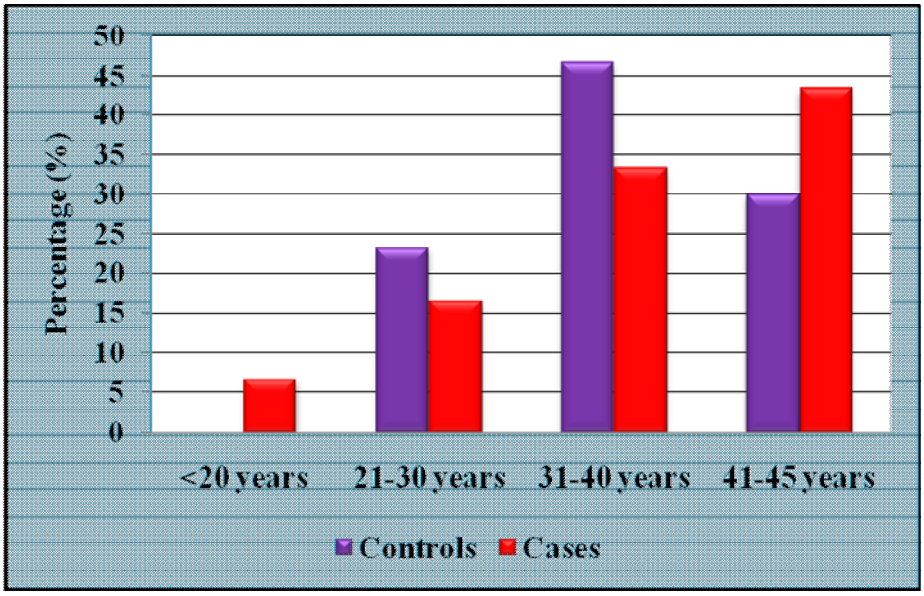


Table-4: According to the above table maximum number of patients presenting with AUB were in the age group of 41-45 years that is 43.3% and 33.3% were in the age group of 31-40 years and the least were in the age group <20 years. But the majority of patients attending the OPD for Complaints other than abnormal uterine bleeding were between 31-40 years.

Table-5: Distribution of number of patients according to occupation in cases and controls groups

Occupation	Group-I (Control)	Group-II (Cases)
House wife	18	18
Employee	09	05
Student	01	04
Unskilled labor	02	03

Graph-13: Distribution of percentage of patients according to occupation in controls and cases groups

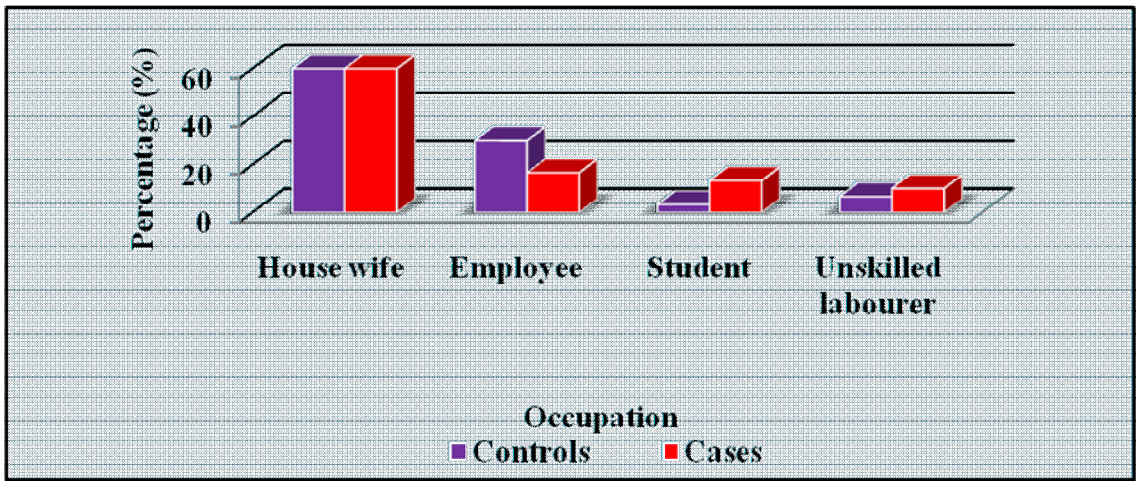


Table-5: In both controls and cases maximum numbers of patients were house wives. Only 4 patients were students among cases and only one student was present in the control group.

Table-6: Distribution of number of patients according to marital status in cases and controls groups

Marital status	Group-I (Control)	Group-II (Cases)
Married	29	26
Unmarried	1	4

Graph-14: Distribution of percentage of patients according to marital status in cases and controls groups

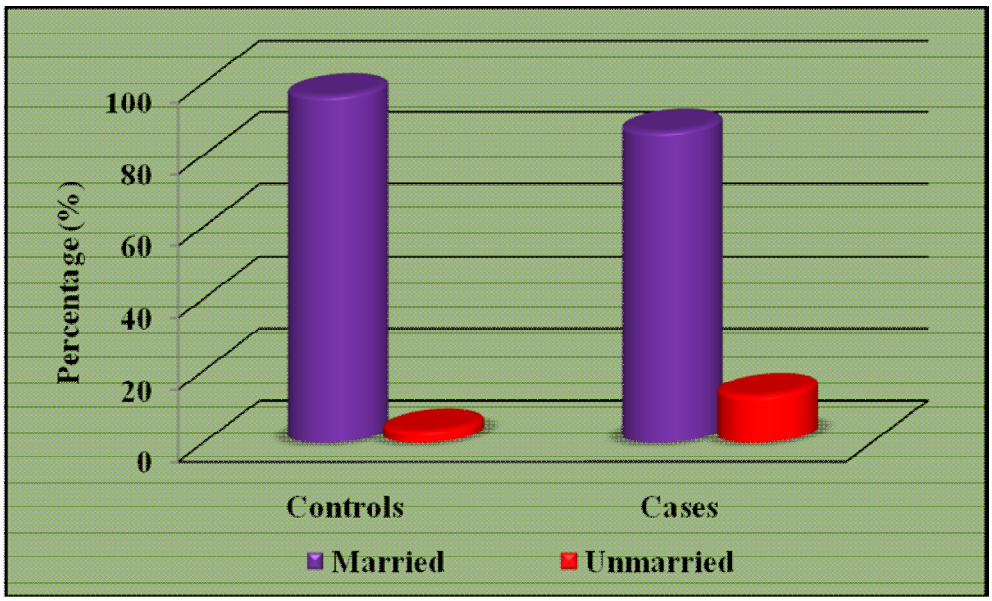
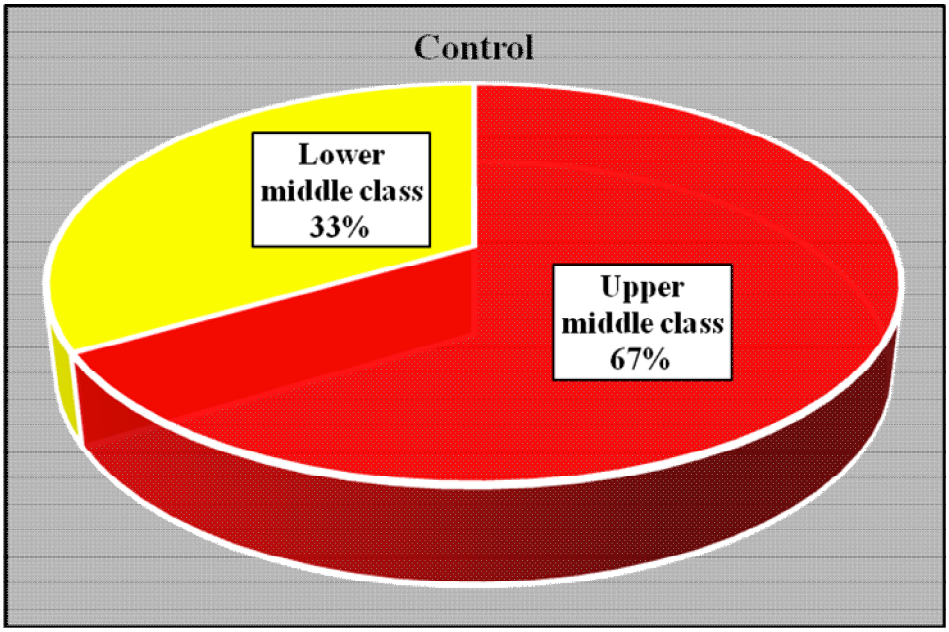


Table-6: Among both controls and cases majority of patients were married.13.3% of women among patients presenting with abnormal uterine bleeding were unmarried as compared to only 3% in the control group

Table-7: Distribution of number of patients according to socio-economic status in cases and controls groups

Socio-economic status	Group-I (Control)	Group-II (Cases)
Upper middle class	20	17
Lower middle class	10	13

Graph-15: Distribution of percentage of patients according to socio-economic status in controls



Graph-16: Distribution of percentage of patients according to socio-economic status in cases

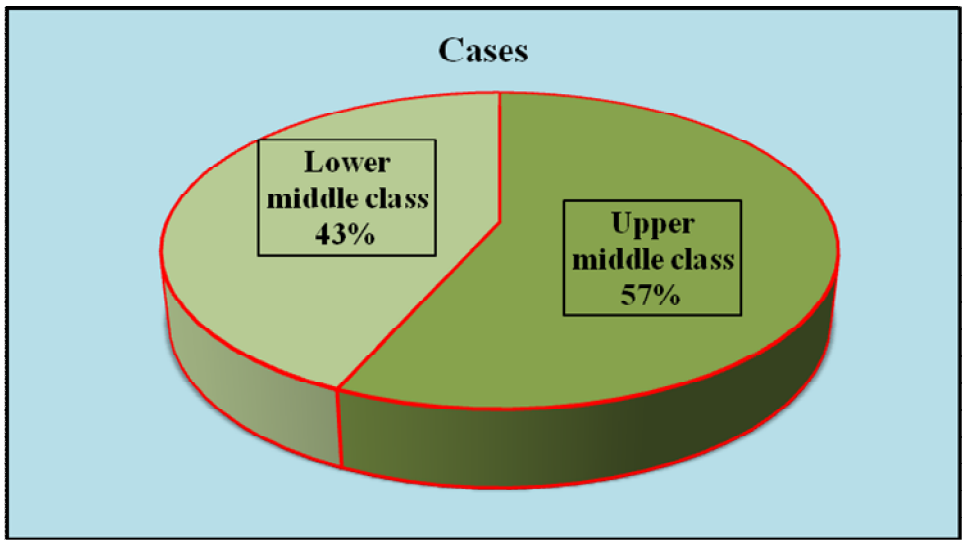


Table-7: Both controls and cases had more number of people in upper middle class than lower middle class. There was lesser number of patients from upper middle class families among cases compared to controls. But the numbers of patients from lower middle class were more among cases than controls.

Table-8: Distribution of number of patients according to nutritional status in cases and controls groups

Nutritional status	Group-I (Control)	Group-II (Cases)
Poor	00	01
Moderate	30	29

Table-8: In the control group all the patients were moderately built and nourished. Among cases only one patient was poorly built and nourished.

Graph-17: Distribution of percentage of patients according to nutritional status in cases and controls groups

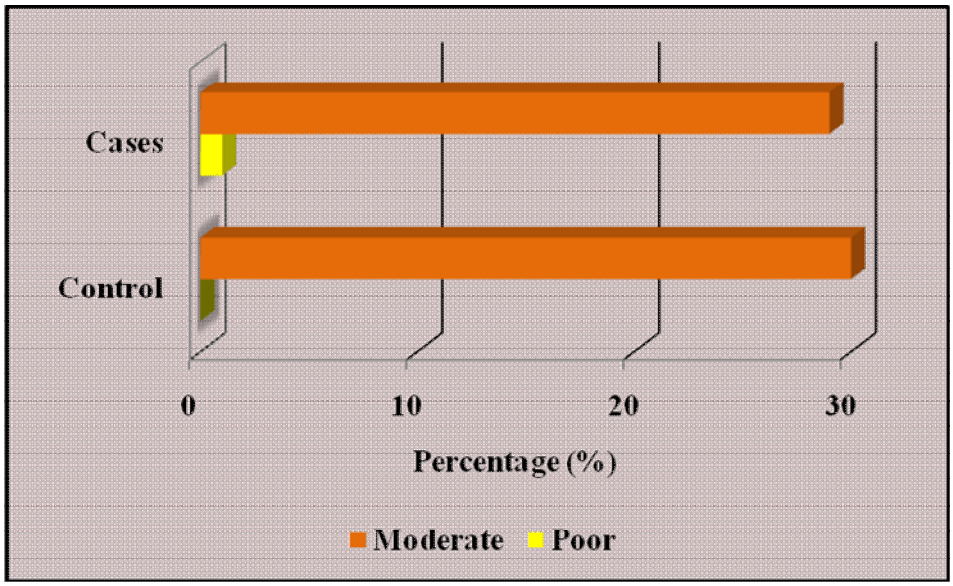


Table-9: Comparison of past history between control and case groups

Past history	Group-I (Control)		Group-II (Cases)	
	Number	Percentage (%)	Number	Percentage (%)
No past medical history	21	70.00	21	70.00
Hypertension	00	00.00	01	03.33
Asthma	03	10.00	02	06.67
Diabetes mellitus	01	03.33	01	03.33
PCOD	00	00.00	01	03.33
Breast lump excision	01	03.33	00	00.00
Ovarian cyst	01	03.33	00	00.00
Suffering from more than one diseases	02	06.67	03	10.00

Table-9: In both groups equal number of subjects had, no relevant past history. 2 in controls and 3 in cases group had more than two diseases. There was no hypertensive, PCOD subjects in control group. No subjects had history of breast lump or ovarian cyst among cases.

Table-10: Comparison of family history between control and case

Family history	Group-I (Control)		Group-II (Cases)	
	Number	Percentage (%)	Number	Percentage (%)
a) No family medical history	23	76.67	22	73.33
b) Hypertension	03	10.00	00	00.00
c) Asthma	00	00.00	01	03.33
d) Diabetes mellitus	00	00.00	04	13.33
e) Hypothyroidism	01	03.33	00	00.00
f) Suffering from more than one diseases	03	10.00	03	10.00

Table-10: 23 in control group and 22 in case group had no relevant family history. There was no family history of bronchial asthma or diabetes in the control group. No family history of hypertension and hypothyroidism in case group. Equal number of patients had family history of more than two diseases.

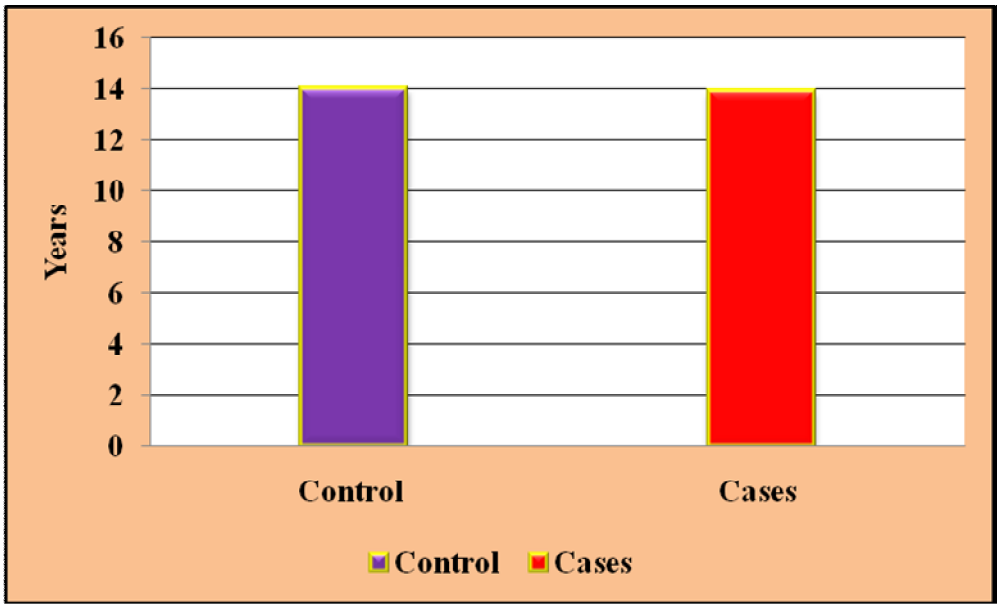
6.2. Menstrual history

Table-11: Comparison of previous menstrual history of cases and control groups

Menstrual history	Group-I (Control) (MEAN±SEM)	Group-II (Cases) (MEAN±SEM)	P values
Age of menarche	14.00±0.22	13.90±0.21	0.786
Duration of cycle (days)	29.57±0.31	31.83±1.43	0.567
Duration of flow (days)	4.13±0.18	5.17±0.28*	0.02

(p < 0.05 significant when duration of flow between controls and cases was compared)

Graph-18: Comparison of mean age at menarche between controls and cases



Graph-19: Comparison of mean duration of menstrual cycles and duration of flow between controls and cases

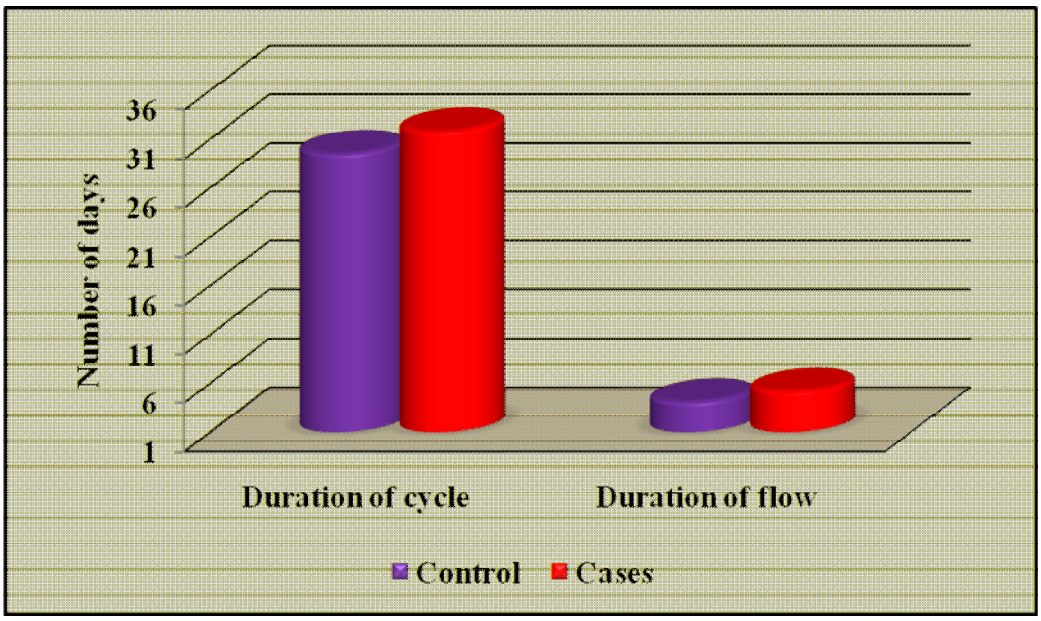


Table-11: No significant difference in mean values for age at menarche, duration of cycle between control and case groups. But duration of flow showed significant difference between controls and cases.

Table-12: Distribution of patients according to amount of flow in cases and controls

Amount of flow	Group-I (Control)		Group-II (Cases)	
	Number	Percentage (%)	Number	Percentage (%)
Scanty	00	00.00	00	00.00
Moderate	30	100.0	30	100.0
Excessive	00	00.00	00	00.00

Table-12: No scanty and excessive flow observed in control and case groups. All the patients had moderate flow.

The above two tables showed that no relation was found between age at menarche, previous cycle length and flow on future progression to abnormal uterine bleeding. But there was significant increase in the number of days of flow in cases compared to controls.

Table-13: Comparison of obstetric history between cases and controls

Obstetric history	Group-I Control (MEAN±SEM)	Case (MEAN±SEM)	P value
Married life	12.65±7.55	15.13±9.17	0.26
Para	0.93±0.98	1.70±0.98*	0.00
Abortion	0.33±0.71	0.07±0.25*	0.05
Last delivery	7.37±7.96	11.83±7.96*	0.03

(*P < 0.05 shows significant difference when mean values of parity, abortions and last delivery were compared between controls and cases, P > 0.05 showed no significant difference when mean married life was compared between controls and cases)

Table-13: The above table shows that there is significant difference in the parity, number of abortions and last child birth between the controls and cases. But years of married life showed no significant difference among the groups. This can be accounted for by the fact that patients presenting with abnormal uterine bleeding were from the older age group compared to that in the control group.

Table-14: Distribution of patients in cases and controls according to Obstetric score

Obstetric score	Group-I (Control)		Group-II (Cases)	
	Number	Percentage (%)	Number	Percentage (%)
Nulli parous	14	46.67	6	20.00
Para 1	5	16.67	5	16.67
Para 2	10	33.33	13	43.33
Para 3	1	03.33	6	20.00

Table-14: 14 Peoples in controls and 6 in cases were nulliparous. Equal number of people had 1 child in case and control groups. 10 in control and 13 in cases had 2 children. Only 1 in control and 6 in case group has 3 children.

Graph-20: Comparison of number tubetomized patients between controls and cases

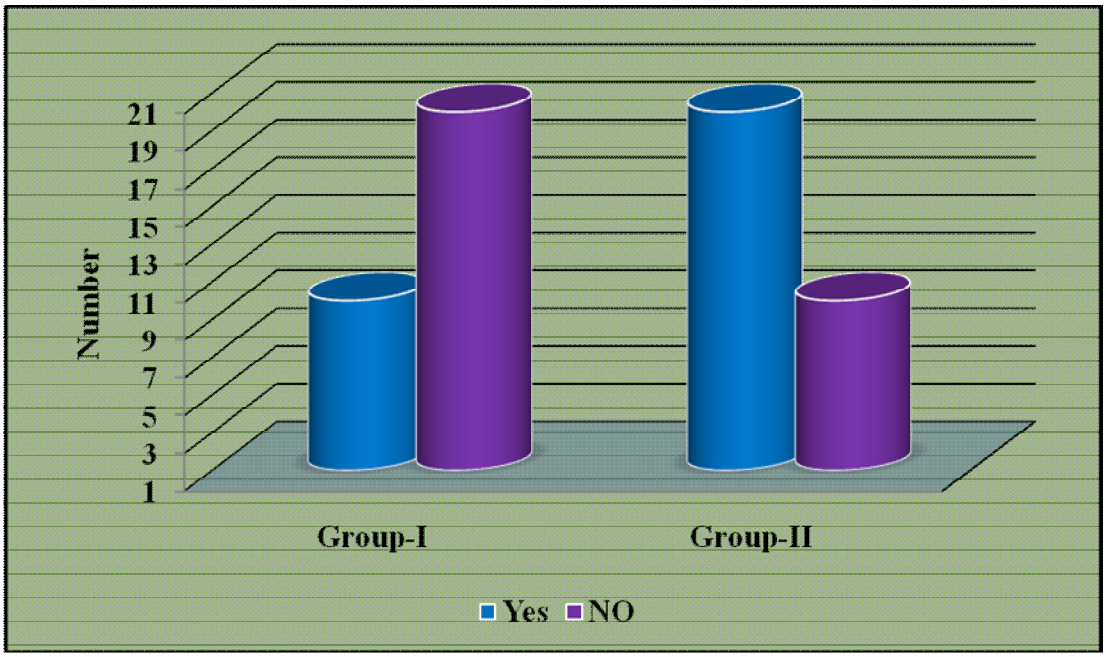


Table-15: Distribution of patients according to per speculum findings in controls and cases

Per speculum examination	Group-I (Control)		Group-II (Cases)	
	Number	Percentage (%)	Number	Percentage (%)
Normal	19	63.33	14	46.67
Cervix unhealthy	11	36.67	11	36.67
Abnormal Discharge	09	30.00	05	16.67
Not done	01	3.33	04	13.33

Table-15: In 1 patient in controls and 4 patients in cases per speculum examination was not done 19 patients among controls and 11 patients among cases had normal per speculum examination. 63% of controls and 46.67% cases had healthy cervices.

Table-16: Distribution of patients according to per speculum findings in the study population

Per speculum examination	Total study population	
	Number	Percentage (%)
Normal	33	55.00
Cervix unhealthy	22	36.67
Discharge	14	23.33
Not done	5	08.33

Table-16: In 8.33% of the population speculum examination was not done. 36.67% of all the 60 patients in the study had unhealthy cervices and 23.3% had abnormal discharge P/V. These points to the importance of complete Gynacecological examination in all patients presenting to the department of Gynaecology.

6.3. General and systemic examination

Table-17: Comparison of pulse rate, systolic and diastolic blood pressure between the controls and cases

Cardiovascular parameter	Group-I Controls (MEAN±SEM)	Group-II Cases (MEAN±SEM)	P value
Pulse rate	73.33±0.65	76.57±1.19*	0.02
Systolic blood pressure	116.13±1.57	113.00±1.98	0.22
Diastolic blood pressure	75.67±1.34	75.33±2.13	0.89

(*P<0.05 was significant when pulse rate between controls and cases were compared, P>0.05 showed no significant difference when systolic and diastolic blood pressure between controls and cases were compared)

Table-17: The above table compares the pulse rate and blood pressure values of both cases and controls. Pulse rate showed significant difference between controls and cases. The systolic and diastolic blood pressure showed insignificant difference.

6.4. Hematological parameters

Table-18: Comparison of hematological parameters between controls and cases

Hematological parameters	Group-I Controls (MEAN±SEM)	Group-II Cases (MEAN±SEM)	P value
Hemoglobin	11.86±0.22	10.39±0.47	0.01*
Platelet count	3.45±0.08	3.60±0.09	0.21
Bleeding time	1.53±0.13	1.63±0.16	0.63
Clotting time	3.90±0.18	3.77±0.20	0.63

(*P<0.05 was significant when hemoglobin level between controls and cases were compared, P>0.05 was not significant when platelet count, bleeding time and clotting time between controls and cases were compared)

Table-18: Only hemoglobin levels showed significant difference between the groups. No significant differences were noted in platelet count, bleeding time and clotting time compared between cases and control. There is a numerical difference in the values but it is not statistically significant.

6.5. Biochemical parameters

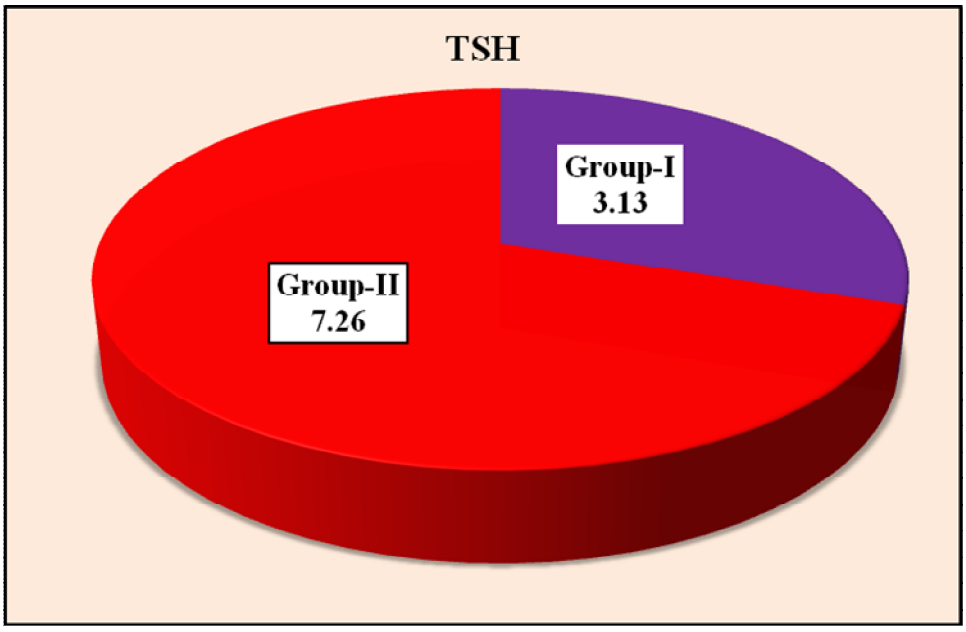
Table-19: Comparison of thyroid profile between controls and cases

Thyroid profile	Group-I Control (MEAN±SEM)	Group-II Case (MEAN±SEM)	P value
TSH	3.13±0.27	7.26±1.99*	0.01
T_3	3.90±0.11	3.95±0.32*	0.02
T_4	14.73±0.46	15.20±1.13*	0.04

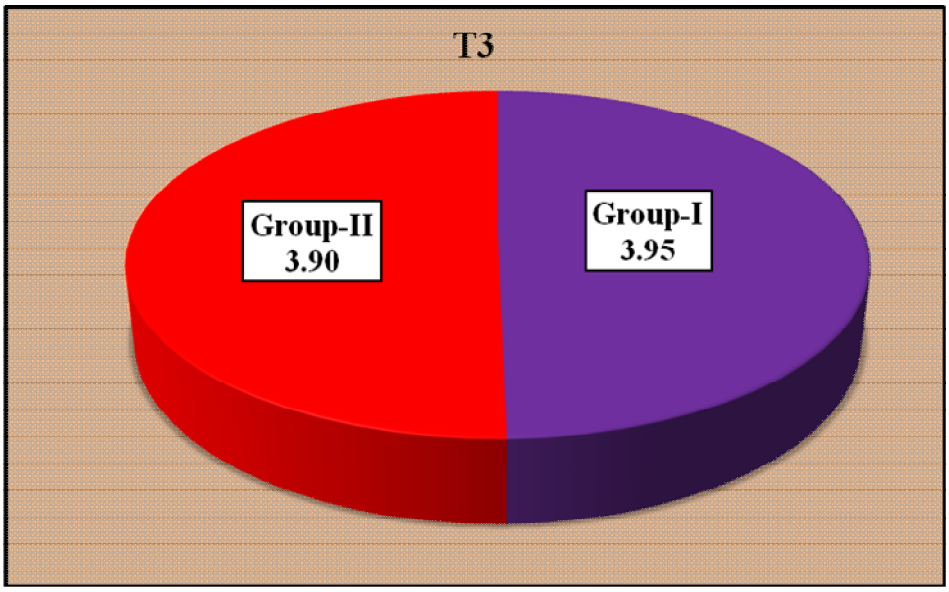
(*P<0.05 significant compared TSH, T_3, T_4control group with cases)

Table-19: Comparison of mean TSH values showed high significant difference compared between the controls and cases the p value was 0.01. T_3, T_4 also showed significant difference when controls and cases were compared. The p values were 0.02 and 0.04 which were statistically significant.

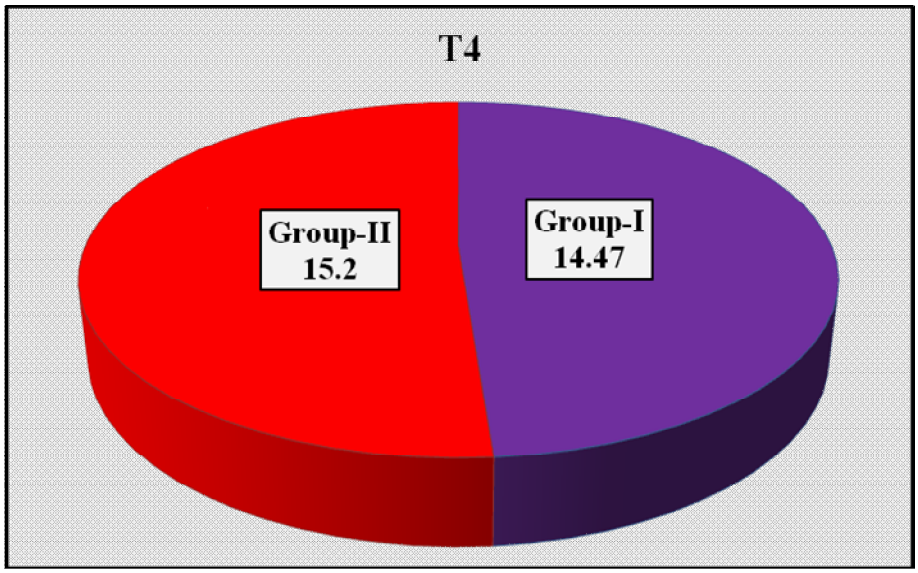
Graph-21: Comparison of mean TSH levels between controls and cases



Graph-22: Comparison of mean T_3 levels between controls and cases



Graph-23: Comparison of mean T_4 levels between controls and cases



6.6. Correlation of menstrual patterns with demographic, hematological and biochemical parameters

Table-20: Distribution of patients according to menstrual pattern in cases group

Menstrual patterns	Group-II (Cases)	
	Number	Percentage (%)
Menorrhagia	13	43.33
PolyMenorrhagia	7	23.33
Metrorrhagia	1	03.33
Menorrhagia with infrequent cycle	3	10.00
Menometrorrhagia	2	06.68
Polymenorrhoea	3	10.00
Oligomenorrhoea	1	03.33
Total	**30**	**100**

Table-20: The above table demonstrates the different menstrual patterns among patients with abnormal uterine bleeding. The commonest pattern was menorrhagia accounting for a total of 43.3% followed by poly menorrhagia in 23.3% of cases. Menorrhagia with infrequent cycles, that is acyclical bleed (anovulatory cycles) were found in 10% of cases ,so also polymenorrhoea in another 10%. The least common patterns were metrorrhagia and oligomenorrhoea.

Table-21: Distribution of number and percentage of hypothyroidism in patients in relation to menstrual patterns in the cases group

S. No	Menstrual patterns	Hypothyroidism	
		Number	Percentage (%)
1.	Menorrhagia	4	57.13
2.	PolyMenorrhagia	1	14.29
3.	Metrorrhagia	1	14.29
4.	Menorrhagia with infrequent cycle	1	14.29
5.	Menometrorrhagia	0	00.00
6.	Polymenorrhoea	0	00.00
7.	Oligomenorrhoea	0	00.00
	Total	7	100

Table-18: The above table demonstrates the menstrual pattern among patients suffering from hypothyroidism. The most common menstrual pattern was menorrhagia accounting for a total of 57.13%. Each of the other patterns like polymenorrhagia, metrorrhagia and menorrhagia with infrequent cycles was seen in 14.29%. No patient with hypothyroidism had menometrorrhagia, polymenorrhoea, or oligomenorrhoea.

Table-22: Distribution of number and percentage of euthyroid patients in relation to menstrual patterns in cases group

S. No	Menstrual patterns	Euthyroid	
		Number	Percentage (%)
1.	Menorrhagia	8	36.36
2.	PolyMenorrhagia	6	27.27
3.	Metrorrhagia	0	00.00
4.	Menorrhagia with infrequent cycle	2	09.09
5.	Menometrorrhagia	2	09.09
6.	Polymenorrhoea	3	13.65
7.	Oligomenorrhoea	1	04.54
	Total	22	100

Table-19: This table demonstrates the pattern of bleed in patients who are euthyroid. Among euthyroid women too the commonest menstrual pattern was menorrhagia (36.6%).This is lesser than that seen in hypothyroid patients where it accounted for 57.13% of cases and a 100% among hyperthyroid patients.the next common menstrual patterns were polymenorrhagia (27.7%) and polymenorrhoea (13.65%).

Table-23: Distribution of cases according to menstrual patterns in relation with thyroid disorder

Menstrual patterns	Hypothyroidism		Hyperthyroidism		Euthyroid	
	Number	%	Number	%	Number	%
Menorrhagia	4	57.13	1	100	8	36.36
PolyMenorrhagia	1	14.29	0	0	6	27.27
Metrorrhagia	1	14.29	0	0	0	00.00
Menorrhagia with infrequent cycle	1	14.29	0	0	2	09.09
Menometrorrhagia	0	00.00	0	0	2	09.09
Polymenorrhoea	0	00.00	0	0	3	13.65
Oligomenorrhoea	0	00.00	0	0	1	04.54
Total	**7**	**100**	**1**	**100**	**22**	**100**

Table-23: The above table demonstrates the menstrual pattern among patients suffering from hypothyroidism. The most common menstrual pattern was menorrhagia accounting for a total of 57.13%. Each of the other patterns like polymenorrhagia, metrorrhagia and menorrhagia with infrequent cycles were seen in 14.29%. No patient with hypothyroidism had menometrorrhagia, polymenorrhoea, or oligomenorrhoea. Among patients with abnormal uterine bleeding only one (3%) patient had hyperthyroidism and this patient had presented with menorrhagia. This table demonstrates the pattern of bleed in patients who are euthyroid. Among euthyroid women too,

the commonest menstrual pattern was menorrhagia (36.6%).This is lesser than that seen in hypothyroid patients where it accounted for 57.13% of cases and a 100% among hyperthyroid patients.the next common menstrual patterns were polymenorrhagia (27.7%) and polymenorrhoea (13.65%).

Table-24: Mean values of thyroid hormone profile in patients with different menstrual pattern

S. No	Menstrual patterns	T3 (MEAN±SEM)	T4 (MEAN±SEM)	TSH (MEAN±SEM)
1.	**Menorrhagia**	5.12±0.75	13.01±2.89	9.39±3.36
2.	**PolyMenorrhagia**	3.76±0.28*	14.28±1.39	6.64±4.42*
3.	**Metrorrhagia**	1.90±0.00*,#	15.25±0.00*	6.73±0.00*
4.	**Menorrhagia with infrequent cycle**	4.29±0.54*,$	14.97±3.04	6.68±5.58*
5.	**Menometrorrhagia**	2.85±0.45*,#,$,ǁ	14.34±3.86$	3.18±1.62*,#,$,ǁ
6.	**Polymenorrhoea**	4.25±0.11*,#,$	15.11±1.76*	2.57±0.62*,#,$,ǁ
7.	**Oligomenorrhoea**	4.16±0.00*,$	16.55±0.00*,#,$,ǁ	1.45±0.00*,#,$,ǁ,ϯ

(*P<0.05 was significant when T_3, T_4 and TSH levels were compared between patients with menorrhagia and others, #P<0.05 was significant when T_3, T_4 and TSH levels between polymenorrhagia patients and others were compared, $P<0.05 was significant when comparing T_3, T_4 and TSH levels between metrorrhagia patients and others, ǁP<0.05 was

significant when comparing T_3, T_4 and TSH levels between patients with menorrhagia and infrequent cycle and others, [1]P<0.05 was significant when T_3, T_4 and TSH levels between polymenorrhoea patients and others were compared)

Table-24: The table above co relates the different menstrual patterns and the levels of various components in thyroid profile. The mean T_3 and TSH values are highest among patients with menorrhagia .But the mean T_4 values are highest among patients with oligomenorrhoea

Table-25: Distribution of patients according menstrual patterns and age

Age (years)	< 20 years	21-30 years	31-40 years	> 40 years
Menorrhagia	0	1	5	7
PolyMenorrhagia	1	2	1	3
Metrorrhagia	0	0	1	0
Menorrhagia with infrequent cycle	2	1	0	0
Menometrorrhagia	0	0	1	1
Polymenorrhoea	0	1	2	0
Oligomenorrhoea	0	0	0	1
Total	**3**	**5**	**10**	**12**

Table-25: Menorrhagia is the commonest menstrual pattern seen in age groups of 31-40 years and >40 years, the older age group. The commonest menstrual pattern in the age group between 21-30 years is polymenorrhagia and in patients <20 years it was menorrhagia with infrequent cycles .This may be due to the anovulatory cycles seen around menarche

Table-26: Distribution of patients with thyroid disorders according to age

Age (years)	**<20 years**	**21-30 years**	**31-40 ears**	**41-45 Years**
Hypothyroidism	1	1	1	4
Hyperthyroidism	0	0	0	1
Euthyroid	2	4	7	9
Total	**3**	**5**	**8**	**14**

Table-26: This table shows the age distribution of patients with thyroid dysfunction. Hypothyroidism is most common in patients >40 years, that is the perimenopausal age group. They account for 57.14% of the hypothyroid patients. The one patient detected to have

hperthyroidsm also comes in the same age group. The rest of the hypothyroid patients were equally distributed among all other age groups.

Table-27: Distribution of menstrual patterns of patients according to TSH levels

Menstrual pattern	Normal (0.39-6.16)	Less than (0.39)	Between (6.17-26.17)	Above 26.17
Menorrhagia	8	1	2	2
PolyMenorrhagia	6		0	1
Metrorrhagia	0	0	1	0
Menorrhagia with infrequent cycle	2	0	1	0
Menometrorrhagia	2	0	0	0
Polymenorrhoea	3	0	0	0

Oligomenorrhoea	1	0	0	0
Total	**22**	**1**	**4**	**3**

Table-27: The 30% of patients with abnormal uterine bleeding73% of patients have normal TSH levels. Among these 36.6% have complaints of menorrhagia and 27.7% polymenorrhagia.3% of patients have TSH less than normal and is associated with menorrhagia.13.3% of patients have mild elevation of TSH, here the commonest menstrual pattern being menorrhagia.10% have very high TSH levels ,here too the commonest pattern being menorrhagia. Therefore total of 23% of patients have high TSH levels.

Table-28: Distribution of menstrual patterns of patients according to T3 and T_4 levels

Menstrual pattern	**T_3**		**T_4**	
	Normal	**Abnormal**	**Normal**	**Abnormal**
Menorrhagia	10	3	10	3
Polymenorrhagia	7	0	6	1
Metrorrhagia	0	1	1	0
Menorrhagia with infrequent cycle	3	0	3	0
Menometrorrhagia	2	0	2	0

Polymenorrhoea	3	0	3	0
Oligomenorrhoea	1	0	1	0

Table-28: The above table correlates T_3, T_4 levels with menstrual pattern. About 13.3% of patients with abnormal uterine bleeding have abnormal T_3, T_4 levels , about 4 out of the total 26 patients. Among these 1patient had lower than normal value. The rest of the 3 had higher than normal values.

From the above two tables it can be concluded that 3% of our patients have hyperthyroidism and 23% have hypothyroidism. But out of the 23%; 13% have only TSH values elevated but normal T_3 , T_4 values, indicating that they have subclinical hypothyroidism. Rests of the 10% have overt hypothyroidism. No cases of sub clinical hyperthyroidism were found.

Table-29: Distribution of patients according to percentage of anemic (mild, moderate, severe) with menstrual pattern

Menstrual pattern	**Normal**	**Less than 8 Anemia**	**8 to 10.9 Moderate Anemia**	**11 to 11.9 Mild anemia**
Menorrhagia	6	2	4	1
PolyMenorrhagia	2	1	3	1
Metrorrhagia	0	0	1	0

Menorrhagia with infrequent cycle	0	2	1	0
Menometrorrhagia	1	0	1	0
Polymenorrhoea	1	0	1	1
Oligomenorrhoea	1	0	0	0
Total	**11**	**5**	**11**	**3**

Table-29: The above table correlates anaemia with bleeding pattern.5 patients (16.6%) of patients had severe anaemia. 11(36.6%) had moderate anaemia and 3 (10%) had only mild anaemia. The rest of the 11 patients (36.6%) had not developed anaemia. The commonest menstrual patterns associated with anemia are menorrhagia and polymenorrhagia, accounted for by the excessive blood loss. Of the 19 anaemic patients 7 had menorrhagia and 4 had poly menorrhagia.

Discussion

7. Discussion

The present study carried out among 30 patients presenting with abnormal uterine bleeding in the age group of 15-45 years. 30 patients who presented to the gynecology department with complaints other than menstrual complaints were taken as controls. Patients with thyroid tomour, on antithyroid medications, h/o recent thyroid surgeries were excluded. Women with any reproductive tract malignancies, organic lesions of the genital tract, IUCD users and bleeding disorders were not included in the study.

In the present study, maximum numbers of patients with abnormal uterine bleeding were in the age group of 41-45 years which accounted for 43.33%. But in the control group about 46.67% were in the age group of 31-40 years. This demonstrates an increasing incidence of menstrual abnormalities in the perimenopausal age group, probably due the increasing number of anovulatory cycles.

In a study by K Padmaleela et. al. in 2011-2012 studied 83 patients in Vishakapatnam, of which 53% patients were within the older age group of 35-45 years. About 31.3% of patients were in the age group of 25-34 years, 33.3% of patients were in the age group of 31-40 years, 16% in the age group of 21-30 years and 6% in the age group <20 years.[81]

In both cases and controls an equal and maximum number of patients were housewives. 4 patients were students among the cases but only one student presented with complaints other than menstrual abnormalities. Most of the women in both cases and controls were married. 13.3 % of women among cases and 3% in controls were unmarried.

There was more number of patients from lower middle class among cases 43% and among controls33%. No patients from poor socioeconomic status were present in this study.

All among controls and most of the patients among cases were moderately built and nourished. Only one patient was poorly built and nourished among cases. There were no obese women in the present study.

70% of the subjects in both cases and controls had no significant past medical and surgical history. Only very few patients in the cases had hypertension or bronchial asthma. One patient had PCOD.

The previous cycles of the patients were compared with the cycles of the control. There was no significant difference in the previous cycle length among the two groups, but there was an increase in the number of days of flow among cases when compared with controls and the values were statistically significant. There may be a relation between present duration of flow and future progression to abnormal bleed. This may suggest a change in the action of normal haemostatic mechanism coming into play towards the end of a menstruation in those with future predisposition to abnormal uterine bleed. This may be due to an inadequate secretion of estrogen derived from the emerging cohort.

In the present study 46.67% of controls and 20% of cases were nulliparous. 43.33% of women were para 2, 20% para 3 and both together were 63.33%. Uniparous women accounted for 16.67% of cases .In the study done by Pahwa. et. al., a majority of patients i.e. 80% belonged to the group para 2 to 4, 4.12% were uniparous and 7% were nulliparous. In a

study by Pilli. et. al. 87% of patients with DUB were multiparous, 7% uniparous and 6% nulliparous. But in the present study 20% of women were nulliparopus.[82]

Among patients with abnormal uterine bleeding, most had vaginal deliveries. This was a lot more than the percentage of vaginal deliveries in controls. The numbers of tubectomised patients among cases were less compared to controls. In the total study population, 36.67% of patients had unhealthy cervix and 23.33% had abnormal discharge. This highlights the importance of complete gynecological examination including per speculum examination in all patients presenting to the gynecology OPD, irrespective of symptoms, so that necessary evaluation can be done.

The comparison of mean values of pulse rates of cases and control showed a significantly higher rate among cases, but blood pressure values seemed unaffected. This may be due to the anemia caused by the abnormal bleed, so also a comparison of the mean hemoglobin levels among cases and controls showed lower hemoglobin values in the cases, owing to the anemia caused by the abnormal uterine bleed, the correction of which is a main factor in management of abnormal uterine bleed. No significant difference was noted in the platelet counts and BT, CT ruling out thrombocytopenia and clotting factor defects in the present study.

The mean T_3, T_4 and TSH values of all the control groups were within normal range. Thus all patients with normal cycles with normal flow were euthyroid. The mean TSH values were high and above the normal range in patients with abnormal uterine bleeding. The mean T_3 and T_4 values were also higher in cases than controls with respective p values of 0.02 and

0.04 which were statistically significant, thus inferring that thyroid dysfunction was more common in patients with abnormal uterine bleeding than in the control group.

In the present study menorrhagia was the commonest abnormal menstrual pattern among cases accounting for about 43.33%, followed by polymenorhagia 23.33%, menorrhagia with infrequent cycles10%, polymenorrhoea 10%, and rest of the patterns like menometrorrhagia 6.68%, metrorrhagia and oligomenorrhoea 3% each. Pilli.et.al. reported 34% menorrhagia as the commonest complaint followed by profuse bleeding following various periods of ammenorrhoea 14% and polymenorrhoea in 11% of cases. Mehrotra. et. al., too showed an incidence of 54.2% of menorrhagia. Pahwa. et. al. observed an incidence of 50% of menorrhagia in patients with DUB, followed by polymenorrhoea 19% and menometrorrahgia in 18%. These studies on abnormal uterine bleed have findings results comparable to our study.[24]

Table 30-Menorrhagia in abnormal uterine bleeding

S. NO	Study type	Percentage (%)
1.	Present study	43.33%
2.	K Padmaleela et al	50.00%
3.	Mehrotia et al	54.20%
4.	Pahwa Sangeetha et al	50.00%
5.	Pilli et al	34.00%
6.	Sharma N et al	70.00%

But in our study polymenorrhagia was the next frequent complaint in 23.33%, where as the second most frequent menstrual pattern varied in different studies.

The most common menstrual pattern in hypothyroid patients in the present study was menorrhagia accounting as high as 57.13%. Hypothyroidism was also associated with menstrual patterns like polymenorhagia, metrorrhagia, menorrhagia with infrequent cycles each accounting 14.7%. In the present study menstrual patterns like oligomenorrhoea, polymenorrhoea and menometrorrhagia were not associated with hypothyroidism.

K Padmaleela. et. al. studied abnormal menstrual patterns in hypothyroid patients. Similar to this study here 53.3% had menorrhagia, 13.3% had polymenorrhoea and another 13.3% had oligomenorrhoea, polymenorrhagia, hypomenorrhoes and ammenorrhoea in 6.7% of patients each. But Pahwa. et. al. demonstrated menorrhagia in as many as 78.94% of patients followed by polymenorrhoea in 10.5%, menometrorrhagia and metropathia haemorrhagica accounted for the rest of the cases (each 5.26%).[81] But a study by Sharma Neelu.et.al. on patients presenting to the endocrinology department in Jammu and Kashmir showed that 44.1% of the hypothyroid patients had normal cycles whereas menorrhagia was found in35.2% cases and polymenorrhoea in another 23.52%.[22]

Table 31-menorrhagia in hypothyroid patients

S. NO	Author Name	Percentage (%)
1.	Present study	57.13%
2.	K Padmaleela et al	53.3%
3.	Kaur et al	64.3%
4.	C Doifode et al	63.3%
5.	Menon and Barucha(menorrhagia and polymenorrhoea)	46.15%
6.	Pahwa et. al.	78.94%

From the findings of this study and other studies it may be suggested that thyroid dysfunction affects the haemostatic mechanisms involved in menstruation, as the menstrual pattern with excessive flow are the commonest patterns associated with thyroid dysfunction.

Only 3% of patients had hyperthyroidism in the present study and the percentage of menorrhagia was100%. In the study conducted by Padmaleela.et.al, among hyperthyroid patients 42.8% had menorrhagia, 28.6% had polymenorrhoea and 14.3% of polymenorrhagia and hypomenorrhoea. Kaur.et.al. had 1 patient with hyperthyroidism who had presented with hypomenorrhoea.[81]

Table 32-menorrhagia in hyperthyroidism

S. No	Author Name	Percentage (%)
1.	Present study	100%
2.	Pahwa et al	100%
3.	Padmaleela et al	42.80%
4.	Sharma N et al	25.00%
5.	Menon and Barucha	17.00%
6.	Singh et al	09.00%

In the study by Singh.et.al oligomenorrhoea was the commonest menstrual pattern 63.6%. Menon and Barucha found oligomenorrhoea in 23.07% of cases .The study by Sharma N showed the commonest pattern as normal cycle (37.5%).[83]

In euthyroid women too the commonest pattern was menorrhagia 36.6%. But hypothyroid patients showed a higher incidence of menorrhagia (57.13%). 100% of hyperthyroid patients had menorrhagia. The next common menstrual patterns were polymenorrhagia 27.27% and polymenorrhoea13.65%

In the present study the patients were grouped according to age as 41-45 years, 31-40 years, 21-30 years, and 20 years and less. Hypothyroidism in these reproductive age group women were seen to increase with advancing age. 57.14% of patients with hypopthyrodism belonged to the age group of 41-45 years (perimenopausal age group).Hypothyroidism in all other age group were similar; 14.7% in each group. The sole patient with hypothyroidism in

the age group15-20 years was 20 years of age. This study had no hypothyroid patients in pubertal age group. In the study conducted by K. Padmaleela.et.al, out of the15 patients with hypothyroidism 66.67 % were in the age group of 35-45 years, 20% between 15-25 years, and 13.33% between 25-34 years.[81] Sharma et. al. also reported a similar 64.7% in the age group of 35-45 years and a 20.58 %and 14.7% in the age groups of 25-34 years and 15-24 years respectively.[22] All the above studies show a similar report of increasing incidence of hypothyroidism with advancing age. But Pahwa.et.al reported a 52.60% of hypothyroidism in the age group of 31-40 years, only 31.6% in the age group of 41-50 years and 15.7% in age group of 20-30 years. The findings of this study were different, probably due to the fact that majority of patients in this study belonged to that age group of 31-40 years.[24]

In this study out of the 30 patients with abnormal uterine bleeding, 13 patients had menorrhagia, of these 53.8% of patients were 41-45 years of age, 38.46 % between 31-40 years and 7.6% were 21-30 years. No patients, under 20 years had menorrhagia. In the next most frequent menstrual pattern of polymenorrhagia, 42.85 % were 41-45 years, 28.57% were 21-30 years and the age groups of 15-20 years and 21-30 years had 14.28% of the patients each. Similarly in the study done by Sharma. N. et. al. the patients with DUB were divided into 2 categories –the menorrhagia , polymenorrhoea group and the oligomenorrhoea, hypomenorrhoea group. 50% of patients with DUB were in the menorrhagia polymenorrhoea group and in the age group of 35-45 years, 20% in the age group of 25-34 years and 8% 15-24 years. 10% of patients with DUB were oligomennorhoea hypomenorrhoea group and were 15-24 years, 8% 25-34 years and 4% 35-45 years of age.[22] The study by Pahwa.et.al, showed a different pattern. 40% of patients with menorrhagia were 31-40 years, 36% were>40 years, 24% were 20-30 years. The next frequent menstrual pattern

was menometrorrhagia, here too 61 % of them were 31-40 years. 22.2%41-50 years and 16.6% 20-30 years. But in their polymenorrhoea group 42% were between 41-50 years. So also in patients with metropathia hemorrhagica 57% were 41-50 years. The major pattern of abnormal uterine bleeding in 15-20 year old patients was menorrhagia with infrequent cycles, probably due to the anovulatory cycles in the few years after menarche.[24]

Table 33-distribution of patients according to thyroid status

Thyroid status	Present study	Pahwa et al	Padmaleela et al	Kaur et al	Neelu Sharma et al
Euthyroid	73.34%	76%	73.5%	85%	64%
Hypothyroid	23.33%	22%	18.1%	14%	22%
Hyperthyroid	3.33%	2%	8.4%	1%	14%

The present study showed that thyroid dysfunction was present in 26.66% of patients presenting to the department of gynecology with abnormal uterine bleeding whereas 73.34% of patients were euthyroid. Hypothyroidism was 7 times more common than hyperthyroidism in the present study. Hypothyroidism was present in 23.33% of cases and hyperthyroidism in 3.33% of cases. The finding of this study was comparable to most other studies.

Padmaleela.et.al. reported 73.15% of euthyroid patients, 18.10% of hypothyroid patients and 8.4% of hyperthyroid patients. Pahwa.et.al. also reported similar results of 22% of hypothyroid and 2% of hyperthyroid cases. Though Neelu Sharma reported similar

percentages of hypothyroidism, she had a much larger percentage of hyperthyroid patients, a 14%. But study was carried out in the Sub Himalayan belt of Jammu.[81]

In the present study, out of the 23% of patients who had hypothyroidism, 13% had subclinical hypothyroidism and 10% had frank hypothyroidism. In this study no cases of subclinical hyperthyroidism were found. In the study by Doifode et al, out of the 28.17% of patients with hypothyroidism 22.3% had subclinical hypothyroidism. In a similar study by Kundu et al, carried out in 100 patients, 13% of patients had sub clinical hypothyroidism.[84]

pIn the present study, 63.33% of patients with AUB had developed anemia .Most of the patients had Hb between 8-10.9 and around 16.6% had Hb <8.The most frequent menstrual patterns associated with anemia,were menorrhagia and polymenorrhagia; the ones with excessive flow.

Conclusion

8. Conclusion

The present study was conducted in patients in reproductive age group presenting with abnormal uterine bleeding (cases) and in patients who presented with complaints other than abnormal uterine bleeding (controls) and thyroid function evaluated in both groups.

- Thyroid dysfunction was found to be much more prevalent in patients with abnormal uterine bleeding (cases) than the controls.
- Among the cases hypothyroidism was more common than hyperthyroidism.
- Unless a proper evaluation of the thyroid function tests are done among these patients,we are bound to miss the etiology of the abnormal bleed leading to nonspecific and ineffective invasive and noninvasive procedures and treatment.

Hence thyroid profile should form an integral part in the evaluation of all patients presenting with AUB and then correction of the thyroid function should be done for efficient and effective treatment.

Summary

9. Summary

The present study was carried out among 60 patients presenting to the department of Gynecology. These patients were selected on the basis of inclusion and exclusion criteria. 30 patients with abnormal uterine bleeding were included in cases; remaining 30 patients with complaints other than abnormal uterine bleeding were included in the control group.

The following observations were made from the present study

- Most of the patients in control group were in the age group of 31-40 years whereas among cases more number of patients were of 41-45 years.
- In both groups most of the patients were house wives. Students were more among cases (4) than the control (1). Maximum number of patients in both groups were married
- There were more number of patients from lower middle class families among cases than in the control group.
- Most of the patients in cases and control groups had no significant past history and family history.
- The previous menstrual history of both cases and controls showed no significant difference in age at menarche and previous cycle length but there was an increased in the number days of flow among the cases. All the parous women in among the cases had normal vaginal deliveries.

- 36% of the study population had unhealthy cervix. 23% had abnormal discharge.
- Cases showed higher pulse rate than controls and hemoglobin values were significantly low. Blood pressure, platelet count, bleeding time and clotting time showed no significant difference.
- Serum T_3, T_4 and TSH levels were within the normal range for all the controls. The cases showed significant difference in all the thyroid parameters.
- 43.33% of patients had menorrhagia and 23.3% had polymenorrhagia. Only 3% patients had oligomenorrhoea.
- The most common menstrual pattern in patients with hypothyroidism was menorrhagia (57.13%). No patients had polymenorrhea, oligomenorrhoea and menometrorrhagia. The patient with hyperthyroidism had menorrhagia.
- Thyroid dysfunction both hypothyroidism and hyperthyroidism was more common in the perimenopausal age group. Only one hypothyroid patient was found in the age group of less than 20 years.
- 3% of patients had less than normal TSH levels and it was associated with menorrhagia. 23 % of patients had high TSH levels and was also associated with menorrhagia. 13% of patients had subclinical hypothyroidism.
- 16.6% of patients had severe anaemia, 36.6% had moderate anaemia. The commonest menstrual patterns among them were menorrhagia and polymenorrhagia.

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Annexures

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Institutional Human Ethics Committee

Ref. No. SMIMS/IHEC/2013/A/17 Date: 1st July 2013

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/A/17,** entitled "Evaluation of Thyroid Profile in Patients with Abnormal Uterine Bleeding" submitted by Dr. Anuradha Prasannan, Postgraduate of Department of Obstetrics and Gynaecology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 30th of May 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCPIGLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
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ABBREVIATIONS

AUB: Abnormal Uterine Bleeding

DUB: Dysfunctional Uterine Bleeding

T_3 : Triiodothyronine

T_4 : Tetraiodothyronine

TSH : Thyroid Stimulating Hormone

TBG : Thyroxine Binding Globulin

MIT: Monoiodothyronine

DIT: Di Iodothyronine

TRH: Thyrotropin Releasing Hormone

RIA: Radio Immuno Assay

SHBG: Sex hormone binding globulin

TFT: Thyroid Function Test

ELISA: Enzyme Linked Immuno Sorbent Assay

SPSS: Statistical Package for Social Sciences

PROFORMA

Evaluation of thyroid profile in abnormal uterine bleeding patients

SERIAL NO: HOSPITAL NO. :
NAME: OCCUPATION:
AGE:
ADDRESS:

1. CHIEF COMPLAINTS:
2. HISTORY OF PRESENTING COMPLAINTS:

A) Bleeding per vagina:

Duration:
Interval:
Quantity: Scanty / Moderate /Excessive
H/o Dysmenorrhoea: Yes /No

B) Other complaints:

3. MENSTRUAL HISTORY:
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. MARITAL HISTORY:

5. OBSTETRIC HISTORY:

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

6. PAST MEDICAL AND SURGICAL HISTORY:

TB / Thyroid disorders/ Bronchial asthma/ RHD/Blood transfusion / H/o Malignancies and treatment details
H/o surgeries / H/o Antithyroid medication.

7. FAMILY HISTORY :

TB / Bronchial asthma / Diabetes mellitus / Hypertension / Genital malignancies / Bleedeing disorders / Thyroid disorders

8. PERSONAL HISTORY:

Diet:
Sleep:
Appetite:
Bowel:
Bladder:

9. SOCIO- ECONOMIC STATUS:

EXAMINATION OF PATIENT:

1. General examination
2. Nutritional Status
3. Pallor
4. Pulse rate
5. Blood pressure
6. CVS
7. Respiratory System

9. PER ABDOMEN:

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

10. VULVO VAGINA EXAMINATION: Healthy / Non Healthy

11. PER SPECULUM EXAMINATION:

12. BIMANUAL VAGINAL EXAMINATION:

13. PERRECTAL EXAMINATION:

14. INVESTIGATIONS:

- Hb % Platelet count
- Urine : Albumin: Sugar: Microscopy:
- BT, CT

15. USG – ABDOMEN PELVIS

16. COMPULSORY

Thyroid function test: a) Serum free T3 b) Serum free T4 c) TSH

CONSENT FORM

PARTICIPANTS CONSENT FORM

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but would help in the advancement of medical sciences. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at tany time without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled "Evaluation of thyroid profile in patients with abnormal uterine bleeding".

Serial no / Reference no

Name of the Participant **Address of the participant**

Contact number of the participant

Signature / thumb impression of the participant / Legal guardian

Witnesses
1.
2.

Date:
Place:

MASTER CHART

Controls								Cases							
S. No	Name	Hospital No	Age (Years)	Marital status	O	SES	Chief complaints	S. No	Name	Hospital No	Age (years)	Marital status	O	SES	Chief complaints
1.	Sothari	886488	32	M	H	L	LAP	1.	Sarala Devi	182919	43	M	E	U	Menorrhagia
2.	Asha	13238953	27	M	H	L	PI	2.	Sudhakumari	184320	45	M	H	U	Polymenorrhagia
3.	Lani	13136100	34	M	E	U	PI	3.	Mary	184895	38	M	H	L	Metrrorhagia
4.	Sasikala	13209185	32	M	H	U	PI	4.	Jayanthi	139239	25	M	U	L	Menorrhagia
5.	Sunitha	13198333	29	M	E	U	SI	5.	Kulsam beevi	185290	45	M	H	U	Menorrhagia
6.	Fathima	131366	38	M	H	U	DP/V	6.	Saraswathi	14001478	28	M	E	L	Menorhagia (with regular and infrequent cycles)
7.	Sudha	13135122	32	M	H	L	DP/V	7.	Sasikala	13207288	31	M	E	U	Menorrhagia
8.	Supriya	13158426	20	UM	S	L	MPA	8.	Aryasree	13193395	15	UM	S	U	Polymenrrhagia
9.	Lalithambika	13216246	30	M	E	L	PI	9.	Thulasi	13170997	41	M	U	L	Menometrorrhagia
10.	Gomathy	13232647	39	M	E	U	PI	10.	Murugam	13157186	40	M	H	U	Menorrhagia
11.	Girija	212138	28	M	H	L	SI	11.	Basumathi	185188	27	M	H	U	Polymenorrhagia
12.	Thulasi	13208124	37	M	H	U	SI	12.	Sumathi	212738	32	M	H	U	Polymenorrhoea
13.	Nisha	191475	29	M	H	U	SI	13.	Mary Kripa	13208071	22	UM	S	U	Polymenorrhoea
14.	Brinalla	13177201	25	M	Ul	L	PI	14.	Naveena	13176623	20	UM	S	U	Menorrhagia (with regular infrequent cycles
15.	Selastin Mary	255529	31	M	E	U	PI	15.	Shyla	13168803	43	M	H	L	Polymenorrhagia
16.	Anitha	13189268	35	M	E	U	PI	16.	Lalitha	13096756	45	M	H	L	Polymenorrhagia
17.	Vijaya Surush	14004075	45	M	H	U	BL	17.	Jalaja	13108494	39	M	H	L	Menorrhagia
18.	Laly	060332	37	M	H	U	RLAP	18.	Nagalakshmi	13131614	36	M	H	U	Menomrorrhagia
19.	Chandra Sheeba	172900	29	M	H	U	SI	19.	Beula	13182215	37	M	E	U	Polymenorrhoea
20.	Anitha M	14005929	33	M	H	U	LAP	20.	Thilakm	13210893	44	M	H	L	Menorrhagia
21.	Grace Evangelin	181583	45	M	H	L	DP/V, LAP	21.	Vasanthi	13171064	42	M	H	L	Menorrhagia
22.	Padmaja Kumari	182278	45	M	H	U	OC (USG)	22.	Sarojini	198606	45	M	H	U	Menorrhagia
23.	Usha	182270	43	M	H	U	LAB	23.	Kala	14002334	35	M	U	L	Menorrhagia
24.	Pavithra	182276	32	M	H	L	PI	24.	Santha Kumari	14008928	43	M	H	L	Menorrhagia
25.	Vijayalakshmi	182237	44	M	H	U	LAP	25.	Mahalakshmi	14008978	38	M	E	L	Polymenorrhagia
26.	Ambika	188402	42	M	E	U	LAP	26.	Menol	13210909	15	UM	S	U	Menorrhagia(with infrequent cycles)
27.	Anjana	188463	42	M	E	U	DIPU	27.	Rethinam	13118109	42	M	H	U	Menorrhagia
28.	Shalini	188562	45	M	H	U	DP/V	28.	Suji Kumari	13192712	30	M	H	U	Polymenorrhagia
29.	Ranjani	188602	42	M	U	L	LAP, DP/V	29.	Nirmala Kumari	13081090	39	M	H	L	Menorrhagia
30.	Shusila	188635	36	M	E	U	RLAP	30.	Sarojini	14002289	45	M	H	U	Oligomenorrhoea

PREVIOUS MENSTRUAL HISTORY AND PAST OBSTETRIC HISTORY

Controls												Cases									
S. No	**Menarche**	**Duration of cycle**	**Amount of flow**	**Duration of flow**	**Dysme**	**Para**	**Type of deliveries**	**Tubecto**	**PH**	**FH**	**S. No**	**Menarche**	**Duration of cycle**	**Amount of flow**	**Duration of flow**	**Dysmen**	**Para**	**Type of deliveries**	**Tubecto**	**PH**	**FH**
1	15	30	MD	2	N	3	ND	Yes	Nil	Nil	**1**	14	30	MD	4	N	2	ND	Yes	Nil	Nil
2	12	30	MD	4	N	0	No	No	Nil	Nil	**2**	12	35	MD	6	N	1	ND	No	HT	DM, HTM
3	14	30	MD	3	N	0	No	No	Nil	Nil	**3**	15	30	MD	7	N	3	ND	Yes	Nil	Nil
4	14	30	MD	4	N	0	No	No	Nil	Nil	**4**	13	28	MD	5	N	1	ND	No	AT	Nil
5	15	30	MD	5	N	1	CS	No	Nil	Nil	**5**	15	30	MD	8	N	1	ND	No	DM	DM
6	14	27	MD	5	N	2	ND	Yes	Nil	Nil	**6**	14	30	MD	6	N	1	ND	No	PCOD	Nil
7	14	30	MD	3	Y	2	ND	Yes	Nil	Nil	**7**	13	30	MD	8	Y	1	ND	No	Nil	Nil
8	14	30	MD	6	Y	0	No	0	Nil	Nil	**8**	13	25	MD	7	N	0	No	No	Nil	Nil
9	16	30	MD	4	N	0	No	No	AT	DM HT	**9**	14	30	MD	4	N	3	ND	Yes	Nil	Nil
10	15	30	MD	5	N	0	No	No	Nil	Nil	**10**	15	35	MD	5	Y	3	ND	Yes	DM, HT	Nil
11	14	30	MD	4	N	0	No	No	Nil	HPT	**11**	15	30	MD	5	Y	2	ND	Yes	Nil	Nil
12	15	25	MD	4	N	0	No	No	Nil	Nil	**12**	14	30	MD	4	N	2	ND	Yes	Nil	Nil
13	13	30	MD	6	Y	0	No	No	Nil	Nil	**13**	14	60	MD	5	N	0	ND	No	Nil	Nil
14	13	30	MD	3	Y	0	No	No	Nil	HT	**14**	12	30	MD	4	N	0	ND	No	Nil	Nil
15	12	32	MD	3	Y	0	No	No	AS	LP, AS	**15**	16	28	MD	5	Y	2	ND	Yes	AT	AT
16	16	30	MD	4	N	0	No	No	Nil	Nil	**16**	16	28	MD	4	N	2	ND	Yes	Nil	Nil
17	16	25	MD	4	N	1	ND	No	BL	HT	**17**	14	30	MD	3	N	2	ND	Yes	Nil	Nil
18	13	30	MD	5	Y	2	ND	Yes	OC	DM ,HT	**18**	14	30	MD	4	N	2	ND	Yes	Nil	Nil
19	13	30	EX	4	Y	0	No	No	EP, LP	Nil	**19**	15	30	MD	4	Y	2	ND	Yes	Nil	Nil
20	13	30	MD	4	Y	2	ND	Yes	DM	Nil	**20**	13	30	MD	5	Y	3	ND	Yes	Nil	DM
21	15	30	MD	4	N	1	ND	No	HT, PT	Nil	**21**	14	30	MD	3	Y	2	ND	Yes	DM, HT	Nil
22	14	30	MD	2	Y	2	CS	No	Nil	Nil	**22**	14	30	MD	4	Y	3	ND	Yes	Nil	Nil
23	16	30	MD	4	Y	2	ND	Yes	Nil	Nil	**23**	14	30	MD	4	Y	2	ND	Yes	Nil	DM
24	13	30	MD	4	Y	0	No	No	Nil	Nil	**24**	14	30	MD	6	Y	3	ND	Yes	Nil	Nil
25	15	26	MD	5	N	2	CS	Yes	AT	Nil	**25**	14	30	MD	7	Y	0	No	Yes	AT	DM, AT
26	13	28	MD	5	Y	2	ND	Yes	Nil	HT	**26**	14	30	MD	8	N	0	No	No	Nil	Nil
27	13	32	MD	5	N	2	ND	Yes	Nil	Nil	**27**	14	28	MD	7	Y	2	ND	Yes	Nil	Nil
28	14	32	MD	4	N	1	ND	No	AD	Nil	**28**	15	28	MD	5	N	2	ND	Yes	Nil	Nil
29	12	30	MD	4	N	1	CS	No	Nil	Nil	**29**	12	30	MD	3	N	2	ND	Yes	AD	DM, HT
30	14	30	MD	5	N	2	ND	Yes	Nil	Nil	**30**	11	60	MD	5	N	0	No	No	Nil	DM

Control						Cases					
S. No	**GE**	**NS**	**PR**	**SBP**	**DBP**	**S. No**	**GE**	**NS**	**PR**	**SBP**	**DBP**
1.	PA	MD	70	110	70	**1.**	PA	MD	76	110	70
2.	PA	MD	80	100	60	**2.**	PA, DS	MD	78	150	100
3.	NL	MD	72	120	80	**3.**	PA	Poor	76	100	60
4.	PA	MD	72	110	90	**4.**	PA, DS	MD	88	110	60
5.	N	MD	72	110	70	**5.**	PA	MD	78	120	80
6.	PA	MD	70	120	70	**6.**	PA, DS	MD	78	110	70
7.	NL	MD	70	100	70	**7.**	DS	MD	72	110	70
8.	NL	MD	70	100	80	**8.**	PA	MD	92	100	60
9.	NL	MD	78	120	80	**9.**	PA	MD	70	110	80
10.	NL	MD	72	120	70	**10.**	PA	MD	80	110	70
11.	NL	MD	70	110	70	**11.**	PA	MD	70	120	80
12.	PA	MD	72	110	70	**12.**	PA	MD	70	100	70
13.	NL	MD	72	110	70	**13.**	NL	MD	78	110	90
14.	NL	MD	76	120	80	**14.**	PA	MD	80	110	70
15.		MD	72	120	80	**15.**	PA	MD	69	110	90
16.		MD	72	100	60	**16.**	PA	MD	72	110	80
17.	PA	MD	72	130	70	**17.**	PA	MD	72	120	70
18.	PA	MD	84	110	70	**18.**	PA	MD	76	110	70
19.	PA	MD	72	120	70	**19.**	PA	MD	70	100	90
20.		MD	72	120	80	**20.**	PA	MD	88	130	90
21.	PA	MD	72	130	90	**21.**	PA	MD	80	120	70
22.		MD	72	120	80	**22.**	DS	MD	78	120	90
23.		MD	76	120	80	**23.**		MD	72	120	90
24.		MD	74	124	82	**24.**	PA	MD	88	100	60
25.	PA	MD	80	120	84	**25.**	PA	MD	72	130	90
26.		MD	72	120	80	**26.**	PA	MD	88	110	60
27.		MD	74	128	78	**27.**	PA	MD	72	110	80
28.		MD	68	122	78	**28.**	PA	MD	72	100	60
29.		MD	74	120	80	**29.**	PA	MD	70	120	70
30.		MD	78	120	78	**30.**		MD	72	110	70

CLINICAL INVESTIGATIONS DATA OF CONTROL AND CASES

Control								Case							
S. No	**HB**	**PC**	**BT**	**CT**	**T3**	**T4**	**TSH**	**S. No**	**HB**	**PC**	**BT**	**CT**	**T3**	**T4**	**TSH**
1.	13	3	2	4	4.45	11.98	3.58	**1.**	13.1	3	1:30	4:30	4.24	18.73	3.04
2.	9.4	3.2	2	5:30	3.82	11.56	4.5	**2.**	9.7	2.9	2:30	4:10	3.28	6.85	32.89
3.	12.6	3	2	3:45	3.41	18.60	2.62	**3.**	9.4	3.2	2:30	0:30	1.90	15.25	6.73
4.	11.6	3.2	1:30	4:30	3.50	11.37	2.97	**4.**	10.0	4	1:30	3:00	3.85	8.85	31.4
5.	13.2	4.1	1:30	4	3.52	15.97	1.85	**5.**	12.5	3.8	1:45	4:20	6.42	19.14	5.78
6.	10	3	1:15	3	5.05	15.00	3.87	**6.**	9.7	2.7	1:46	4:35	4.59	10.52	1.09
7.	12.7	3.8	2:30	6:30	4.44	15.15	2.05	**7.**	13.2	4.02	1:30	4:30	3.09	14.10	4.23
8.	11.8	3.8	1:45	4	4.24	19.02	2.35	**8.**	6.90	4.02	3:30	4:30	5.03	14.23	3.58
9.	12.3	3.8	2:15	3:30	3.5	17.3	9.0	**9.**	10.6	3.94	1:30	4:00	2.40	18.20	4.80
10.	13.1	4	2	5:30	5	12.07	3.1	**10.**	8.2	3.96	1:45	3:30	1.03	7.9	15.61
11.	13.2	4	1:30	4:30	4.22	17.7	1.91	**11.**	11.5	3.4	1:30	6:00	3.75	15.29	1.31
12.	10.6	3.4	1:13	3:30	3.32	11.88	2.63	**12.**	11.5	3.84	3:00	5:51	4.48	12.18	3.58
13.	11	2.8	1:30	4:30	3.94	17.56	2.21	**13.**	12.0	3.82	3:56	4:28	4.19	14.89	2.69
14.	12.8	3.54	1:30	5	4.76	17.67	3.58	**14.**	4.9	4.52	2:86	3:29	3.25	13.61	17.83
15.	12	4	1:30	3:30	2.94	15.41	1.39	**15.**	8.9	4	2:1	3:45	3.47	17.50	0.66
16.	12.6	3.4	1:50	5:30	3.84	20.16	1.49	**16.**	10.8	3.67	3:48	4:08	3.70	14.24	4.77
17.	9.3	3.67	1:45	3:30	4.63	15.42	3.63	**17.**	11.8	3.8	1:30	4:00	5.29	18.84	2.52
18.	11	3.48	1:45	5	4.2	12	3.6	**18.**	12.8	3.24	1:30	4:00	3.29	10.48	1.56
19.	12.6	3.45	1:30	3:30	4	11.8	4.6	**19.**	10	3.9	1:30	4:30	4.08	18.25	1.45
20.	12.2	4	1:45	3:45	2.71	14.08	1.47	**20.**	9.90	3.6	3:56	4:21	3.31	16.01	1.79
21.	13.6	3.2	3:30	6	4.08	12.33	2.14	**21.**	6.1	3.02	2:86	3:08	10.92	40.27	0.01
22.	13.1	4	3	5	3.84	14.92	2.8	**22.**	12.9	3.98	1:30	4:30	3.45	13.20	18.60
23.	11.4	2.48	1:45	3:48	3.92	16.74	2.23	**23.**	12.8	4	3:56	4:21	3.21	12.86	1.01
24.	12	3.48	1:30	3:30	2.8	15	1.4	**24.**	3.3	2.14	1:08	1:45	5.00	12.67	0.87
25.	9	3	1:04	3:03	4.4	15	3.8	**25.**	11.8	2.84	1:30	4:00	2.77	13.71	0.43
26.	11	3.2	1:04	3:05	3	12	4.6	**26.**	8.0	4.18	1:45	4:00	5.03	20.78	1.12
27.	12	3.2	2	3:08	4.4	14.2	2.8	**27.**	12.0	3.94	1:30	4:30	3.64	18.70	1.40
28.	12.8	3.6	3:28	5:02	3.2	14	4.2	**28.**	12.0	3.84	3:49	4:26	4.31	18.11	3.06
29.	11.8	3.68	3	4:08	4	12	4.4	**29.**	10.8	3.6	1:30	5:00	1.44	3.97	42.72
30.	12	3	2	3:04	4	14	3	**30.**	14.5	3.24	1:30	5:00	4.16	16.55	1.45

KEY TO MASTER CHART

[O- OCCUPATION, SCS – SOCIOECONOMIC STATUS, LAP – LOWER ABDOMINAL PAIN, PI – PRIMARY INFERTILITY, SI – SECONDARY INFERTILITY, M – MARRIED, UM – UNMARRIED, H – HOUSE WIFE, E – EMPLOYED, S – STUDENT, U – UPPER MIDDLE CLASS, L – LOWER MIDDLE CLASS, MD – MODERATE, PH – PAST HISTORY,FH – FAMILY HISTORY, MD – MODERATE, EX – EXCESSIVE, ND – NORMAL DELIVERY, CS – CAESAREAN SECTION,Y – YES,N – NO,DM – DIABETES MELLITUS, HT-HYPERTENSION,AT – ASTHMA,PA – PALLOR,NL – NORMAL, SBP– SYSTOLIC BLOOD PRESSURE, DBP – DIASTOLIC BLOOD PRESSURE, PR – PULSE RATE,HB – HEMOGLOBIN,PC – PLATELET COUNT,BT – BLEEDING TIME,CT – CLOTTING TIME]