"HISTOPATHOLOGICAL STUDY OF ENDOMETRIUM IN PATIENTS PRESENTING WITH ABNORMAL UTERINE BLEEDING."

By

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LIST OF ABBREVIATIONS USED

AH	Atypical Endometrial Hyperplasia
AUB	Abnormal Uterine Bleeding
BMI	Body Mass Index
DNA	Deoxyribonucleic Acid
EC	Endometrial Carcinoma
EH	Endometrial Hyperplasia Without Atypia
EHA	Endometrial Hyperplasia with Atypia
EIC	Endometrial Intraepithelial Carcinoma
EIN	Endometrial Intraepithelial Neoplasia
FIGO	International Federation of Gynaecology and Obstetrics
H&E	Haematoxylin and Eosin
HRT	Hormone Replacement Therapy
IHC	Immunohistochemistry
LNM	Lymph Node Metastatsis
MRD	Medical Records Department
NE	Normal Endometrium
NEEC	Non endometrioid Carcinomas
PI	Proliferative Index
PNI	Perineural Invasion
POD	Postovulatory Day
SEIC	Serous Endometrial Intraepithelial Carcinoma
WHO	World Health Organisation

ABSTRACT

"HISTOPATHOLOGICAL STUDY OF ENDOMETRIUM IN PATIENTS PRESENTING WITH ABNORMAL UTERINE BLEEDING"

BACKGROUND- Women suffer from many gynaecological disorders one of them is abnormal uterine bleeding. AUB is a major gynaecological problem in many peri and post menopausal women for which they undergo hysterectomies usually without a definitive diagnosis. So it becomes mandatory to confirm the histomorphology of the lesion, so that medical treatment or conservative surgery can be offered and unnecessary radical surgeries can be avoided. Dilatation and curettage is the most commonly used procedure to diagnose endometrial pathologies.

OBJECTIVES- To evaluate various histopathological features obtained by dilatation and curettage in patients presenting with abnormal uterine bleeding.

METHODOLOGY- The present study was a prospective as well as retrospective study (One year observational study), was done in Department of Pathology from January 2019 to December 2020 at KLE'S DR PRABHAKARKORE HOSPITAL , Belagavi , Karnataka.

It included 50 patients who underwent dilatation and curettage for abnormal uterine bleeding.

Tissues were kept in 10% formalin and processed, followed by paraffin embedding. Hematoylin and eosin (H&E) stained slides available from the department of pathology were studied for histopathological features.

The data was obtained using the SPSS software and regression and correlation analysis was done.

RESULTS-Among 50 cases, it was observed that1(2%) case showed chronic endometritis,2 cases(4%) showed pill endometrium, 26 cases(52%) showed simple hyperplasia without atypia,5 cases(10%) showed complex hyperplasia without atypia, 3 cases(6%) showed complex hyperplasia with atypia,6 cases(12%) of endometrial polyp and7 cases(14%) of endometrial carcinoma**.** Of these 7 cases , 4 cases were of endometrioid adenocarcinoma,2 cases of endometrioid adenocarcinoma with squamous metaplasia and 1 case showed adenosquamous carcinoma.

CONCLUSION-Abnormal uterine bleeding is a common and debilitating condition in women. Endometrial biopsy could be effectively used as the first diagnostic step in AUB and thus ensures correct management.

KEYWORDS-Dilatation and curettage, Histopathology, Endometrium

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INTRODUCTION

Endometrium is a highly active, hormonally sensitive and responsive tissue which constantly and rhythmically undergoes changes during reproductive life of a woman.[1] Women suffer from many gynaecological diseases one amongst them is abnormal uterine bleeding. AUB is one of the commonest complaint for which a woman seeks advice in the gynaecological out patient department. It is defined as any bleeding that doesnot correspond with the frequency, duration or amount of blood flow of a normal menstrual cycle and could be a sign of a simple hormonal imbalance or a serious underlying condition necessitating aggressive treatment including a major surgical procedure.[2]The causes of AUB can be grouped into-

A. Organic causes such as infections of the genital tract, benign and malignant tumors, endometriosis, adenomyosis or because of any iatrogenic causes.

B. Anovulation or oligoovulation which is responsible for majority of the cases. The above mentioned condition resulting in excessive estrogen production leading to continuous stimulation of the endometrial lining and increases the risk of endometrial hyperplasia and carcinoma. Abnormal uterine bleeding can occur during lifespan of a woman at anytime from menarch, occasionally even after menopause in ovulatory and anovulatory cycles.[3] The presenting complaints of the patients can be: spotting, intermenstrual bleeding, bleeding after intercourse, bleeding after menopause, bleeding heavier or for more days than the regular flow/days. Now a days medical advancements combined with inceasing awareness about gynaecological problems women gain access to most of the diagnostic and therapeutic modalities.[4] About 25-30% of abdominal hysterectomies are done for abnormal uterine bleeding.[5] So,it becomes necessary to confirm that whether the lesion is benign or malignant so that proper medical treatment or

conservative surgery can be offered rather than going for an unnecessary radical surgery. Histopathological examination of the endometrium through dilatation and curettage is considered as the most commonest used method to assess the endometrium. It is safe, relatively easy to perform and can be done as a day care procedure.[6]

OBJECTIVE

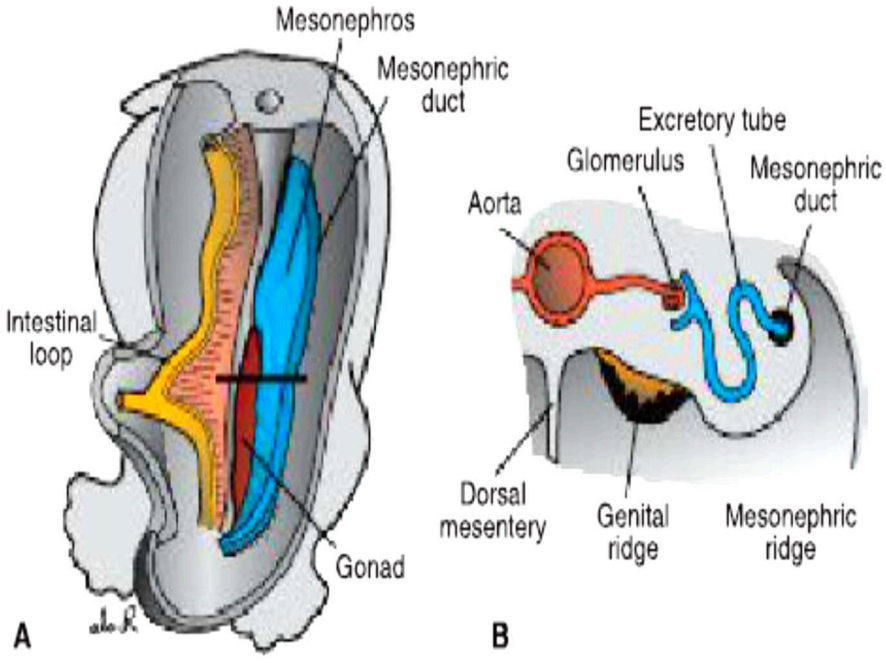
To evaluate various histopathological features obtained by dilatation and curettage in patients presenting with Abnormal Uterine Bleeding.

REVIEW OF LITERATURE

EMBRYOLOGY

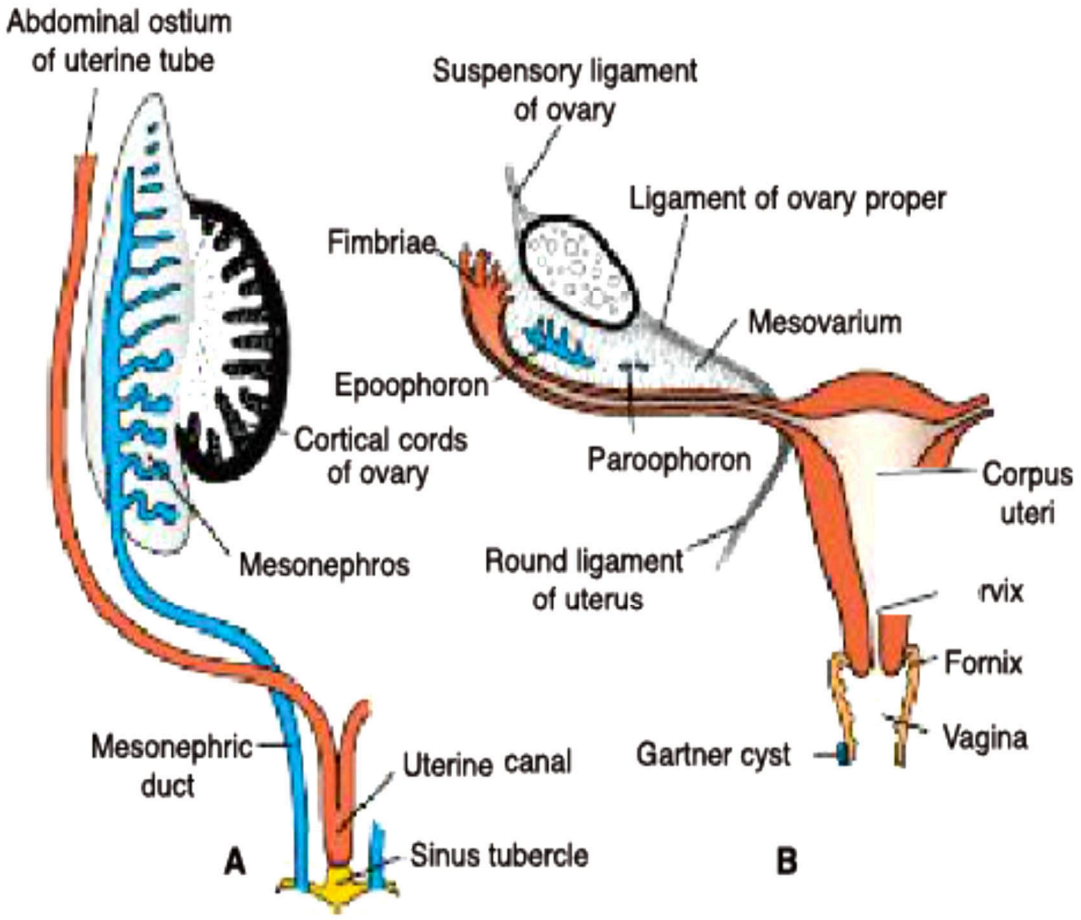
Functionally, the urogenital system can be divided into two entirely different components: the urinary system and the genital system. Embryologically and anatomically, however, they are intimately interwoven. Both develop from a common mesodermal ridge (intermediate mesoderm) along the posterior wall of the abdominal cavity.[7]

Gonads appear initially as a pair of longitudinal ridges, the genital or gonadal ridges. They are formed by proliferation of the epithelium and a condensation of underlying mesenchyme. Germ cells do not appear in the genital ridges until the sixth week of development.[7]



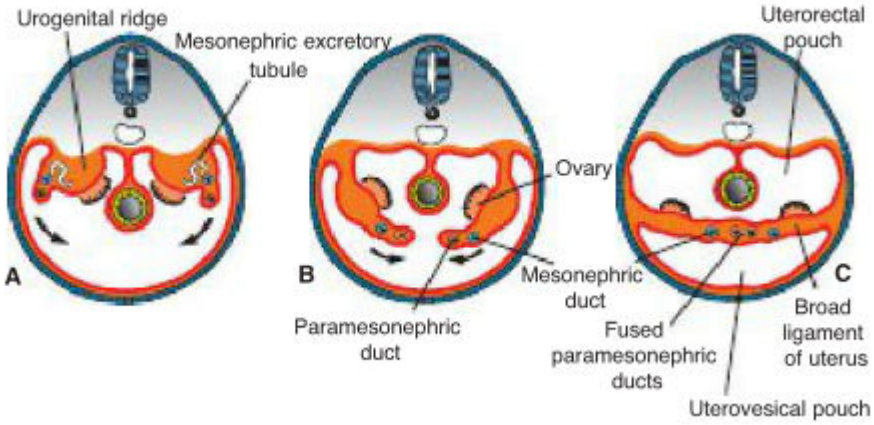
Initially, both male and female embryos have two pairs of genital ducts: mesonephric (Wolffian) ducts and paramesonephric (mullerian) ducts. The paramesonephric duct arises as a longitudinal invagination of the epithelium on the anterolateral surface of the

urogenital ridge. Cranially, the duct opens into the abdominal cavity with a funnel-like structure. Caudally, it first runs lateral to the mesonephric duct, then crosses it ventrally to grow caudomedially. In the midline, it comes in close contact with the paramesonephric duct from the opposite side. The caudal tip of the combined ducts projects into the posterior wall of the urogenital sinus, where it causes a small swelling, the sinus tubercle.The mesonephric ducts open into the urogenital sinus on either side of the tubercle.[7]



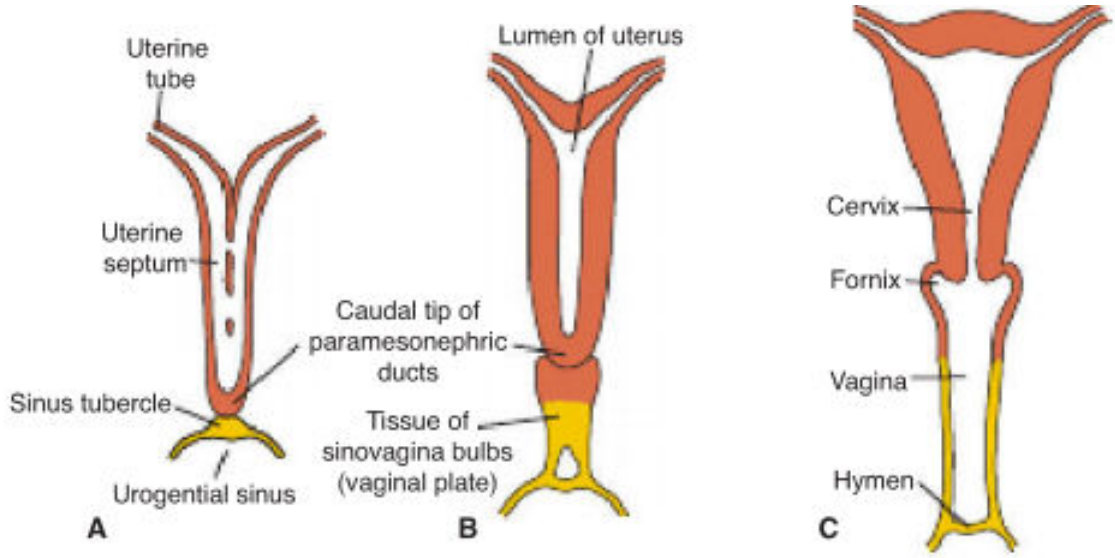
In the presence of estrogen and the absence of testosterone and AMH (MIS), paramesonephric ducts develop into the main genital ducts of the female. Initially, three parts can be recognized in each duct: (1) a cranial vertical portion that opens into the abdominal cavity,(2) a horizontal part that crosses the mesonephric duct, and (3) a caudal vertical part that fuses with its partner from the opposite side.[7]

With descent of the ovary, the first two part develop into the uterine tube, and the caudal parts fuse to form the uterine canal. When the second part of the paramesonephric ducts moves mediocaudally, the urogenital ridges gradually come to lie in a transverse plane. After the ducts fuse in the midline,a broad transverse pelvic fold is established. This fold, which extends from the lateral sides of the fused paramesonephric ducts toward the wall of the pelvis, is the broad ligament of the uterus. The uterine tube lies in itsupper border, and the ovary lies on its posterior surface.The uterus and broad ligaments divide the pelvic cavity into the uterorectal pouch and the uterovesical pouch. The fused paramesonephric ducts give rise to the corpus and cervix of the uterus and the upper portion of the vagina. The uterus is surrounded by a layer of mesenchyme that forms both its muscular coat, the myometrium, and its peritoneal covering, the perimetrium.[7]



Shortly after the solid tip of the paramesonephric ducts contacts the urogenital sinus, two solid evaginations grow out from the pelvic part of the sinus. These evaginations, the sinovaginal bulbs, proliferate and form a solid vaginal plate. Proliferation continues at the cranial end of the plate, increasing the distance between the uterus and the urogenital sinus. By the fifth month, the vaginal outgrowth is entirely canalized. The wing-like

expansions of the vagina around the end of the uterus, the vaginal fornices, are of paramesonephric origin. Thus, the vagina has a dual origin, with the upper portion derived from the uterine canal and the lower portion derived from the urogenital sinus. The lumen of the vagina remains separated from that of the urogenital sinus by a thin tissue plate, the hymen, which consists of the epithelial lining of the sinus and a thin layer of vaginal cells.[7]



ANATOMY

Female reproductive organs include internal and external genital organs. The internal genital organs comprise a pair of ovaries,a pair fallopian tubes, uterus and vagina.[8]

DEFINITION

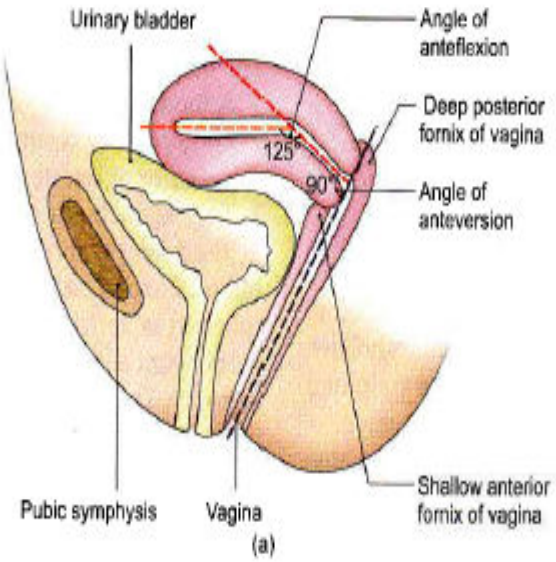
Uterus is a child bearing organ in ,situated in the pelvis between bladder and rectum.It is thick walled and firm, hollow and can be palpated bimanually during a per vaginal examination. It provides and protects a fertilized ovum till it develops into a fully formed foetus.[8]

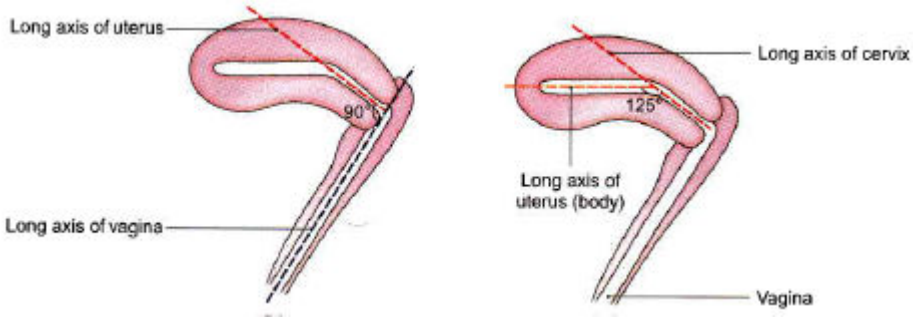
SIZE AND SHAPE

The uterus is pyriform in shape,7.5cm long,5cm broad ,2.5cm thick and weighs around 30-40gms.It is divided into an upper expanded part called body and a lower cylindrical part called the cervix.The junction of these two marks the isthmus.[8]

POSITION AND ANGULATION

Normally, the long axis of the uterus forms an angle of about 90 degrees with the long axis of the vagina. The forward tilting of the uterus relative to the vagina is called anteversion. The backward tilting is called retroversion.[8]





PARTS OF UTERUS

The uterus comprises of-

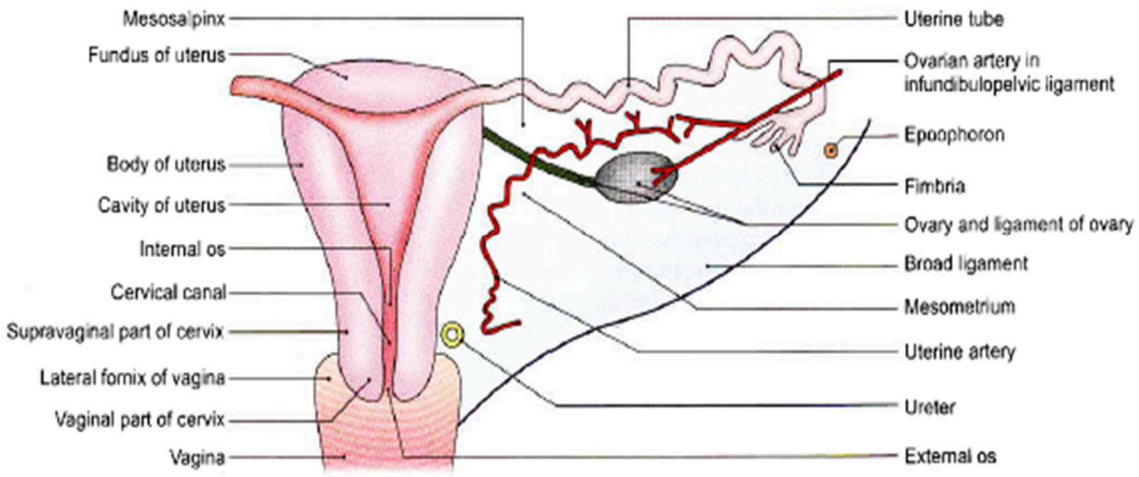
1. A Fundus
2. Body
3. Two lateral borders
4. Cervix

The fundus is formed by the upper end of the uterus. It is covered with peritoneum and is directed forward when the bladder is empty. The fertilized oocyte is implanted in the posterior wall of the fundus.[8]

The anterior surface of the body is flat and is related to the bladder.

The posterior surface is related to the coils of the terminal ileum and to the sigmoid colon.

Each lateral border provides attachment to the broad ligament of the uterus which connects it to the lateral pelvic wall.[8]



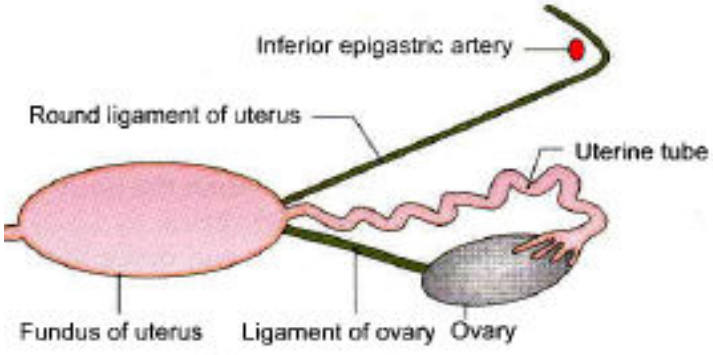
LIGAMENTS OF UTERUS-PERITONEAL

These are just peritoneal folds which do not provide and support to the uterus.

1. The anterior ligament consists of the uterovesical fold of the peritoneum.

2. The posterior ligament consist of the rectovaginal fold forming rectovaginal pouch of the peritoneum.

3. The right and the left broad ligaments are folds of peritoneum that attach the uterus to the lateral pelvic wall.[8]

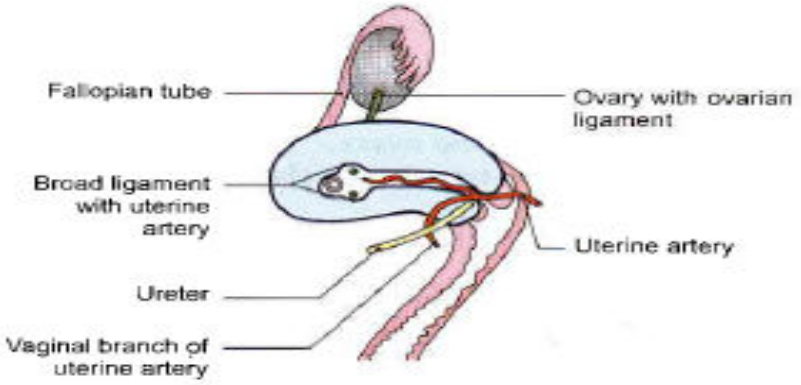


ARTERIAL SUPPLY

The uterus is supplied by-

1. The two uterine arteries.

2. And partly by the ovarian arteries.

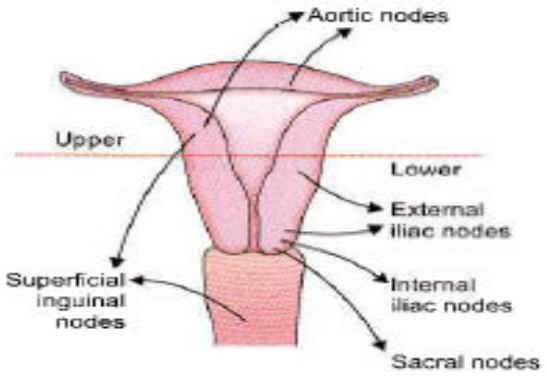


VENOUS DRAINAGE

The veins form a plexus along the lateral border of the uterus.The plexus drains through the uterine, ovarian and vaginal veins into the internal iliac veins.[8]

LYMPHATIC DRAINAGE

Lymphatics of the uterus begin at three intercommunicating networks, endometrial, myometrial and subperitoneal. These plexuses drain into lymphatics on the side of the uterus .Of theses ,the upper lymphatics from the fundus and upper part of the body drain mainly into the aortic nodes and only partly into the superficial inguinal lymph nodes. The lower lymphatics from the cervix drain into the external iliac, internal iliac ad sacral nodes. The middle lymphatics from the lower part of the body drain into the external iliac nodes.[8]



NERVE SUPPLY

The uterus is supplied by both sympathetic from(T12,L1) and parasympsthetic nerves(S2-S4),through the hypogastric and ovarian plexuses.[8]

HISTOLOGY

The female reproductive system has six major functions:

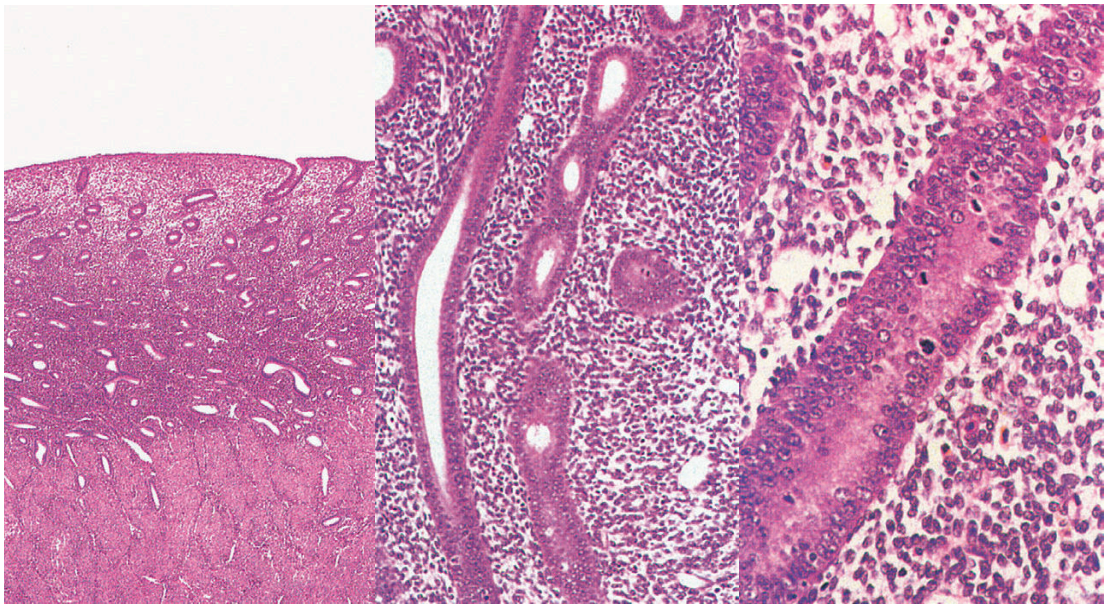
- Production of female gametes, the ova, by the process of oogenesis
- Reception of male gametes, the spermatozoa
- Provision of a suitable environment for the fertilization of ova by spermatozoa
- Provision of an environment for the development of the fetus
- Expulsion of the developed fetus to the external environment
- Nutrition of the newborn

The uterusis a muscular organ, the mucosal lining which undergoes cyclical proliferation under the influence of hormones. This provides a suitable environment for implantation of the fertilised ovum . At birth(parturition), strong contractions of the uterine wall expels the fetus through the lower part of the uterus, the uterine cervix into the birth canal.[9]

In the non-pregnant state, the female reproductive system undergoes changes from puberty to menopause. When ovulation is not followed by the implantation of a fertilised ovum, the thickened mucosal lining, the endometrium, degenerates and a new ovulation cycle starts. In humans, the endometrium is shed in a period of bleeding known as menstruation. The first day of bleeding marks the beginning of a new cycle of endometrial proliferation which is known as menstrual cycle. In humans, the normal menstrual cycle is of 28 days duration.[9]

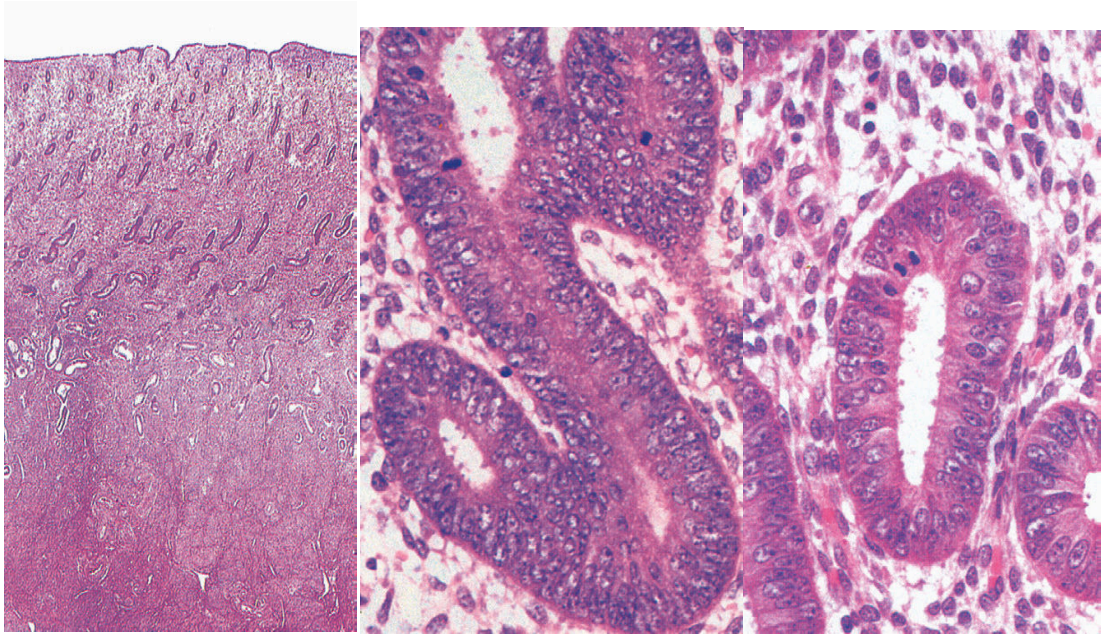
PROLIFERATIVE PHASE

The image below shows proliferative endometrium at low magnification. The bottom of the field includes part of the muscular wall, the myometrium . The relatively thin endometrium consists of the stratum basalis ,stratum spongiosum and stratum compactum. The glands at this stage are sparse and straight. As the glands, vessels and stroma proliferate, the endometrium gradually becomes thicker. By day 5 to 6 of the cycle, the surface epithelium has regenerated. During the proliferative phase, the epithelial cells acquire microvilli , cilia as well as the cytoplasmic organelles required for the secretory phase. In the next image the straight tubular form of the endometrial glands can be seen. At very high magnification, the proliferating glandular epithelium is seen to consist of columnar cells with basally located nuclei having prominent nucleoli. Mitotic figures can be seen, both in the epithelium and stroma.[9]



By the late proliferative stage, the endometrium has doubled in thickness. In contrast to the stratum functionalis, the appearance of the stratum basalis is little changed when compared with the early proliferative phase. The next image shows that the tubular glands

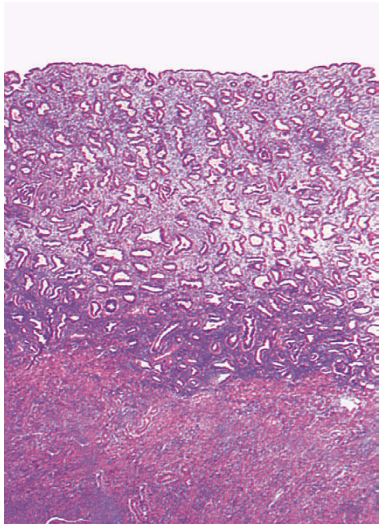
have now become coiled and more closely packed. At very high magnification ,mitotic figures are seen in both the glandular epithelium and the stroma. The stroma is also somewhat oedematous at this stage. Lymphocytes and few lymphoid aggregates are a normal feature of late proliferative phase.[9]

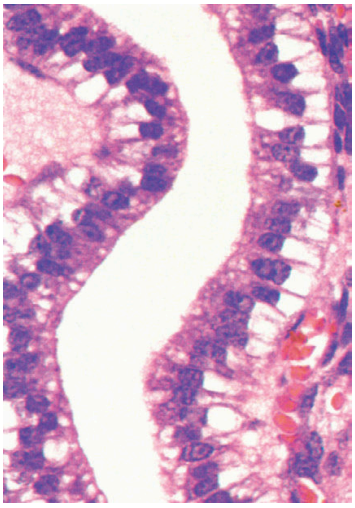


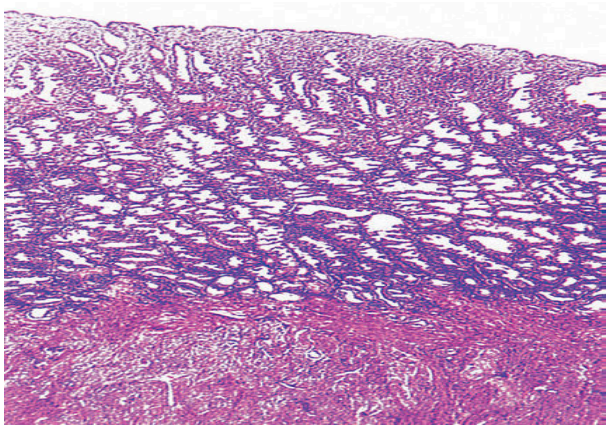
SECRETORY PHASE

Ovulation marks the onset of the secretory phase. At low magnification , the coiled appearance of the glands is more pronounced and the endometrium approaches its maximum thickness. Under the effect of progesterone, the glandular epithelium is stimulated to synthesize glycogen. Initially, the glycogen accumulates to form vacuoles in the basal aspect of the cells, thus displacing the nuclei towards the centre of the tall columnar cells. The basal vacoulation of the cells appears on day 16 and is the characteristic feature of early secretory endometrium . Glycogen is an important source of nutrition for the fertilised ovum. The late secretory phase is characterised by a saw-tooth appearance of the glands, containing copious thick glycogen- and glycoprotein-rich secretions .At very high magnification , the cytoplasmic vacuoles can now be seen on the

luminal aspect of the cell, and the nucleus has returned to its basal position. Mitotic figures are absent. The stroma is at its most vascular and interstitial fluid begins to accumulate between the stromal cells.[9]



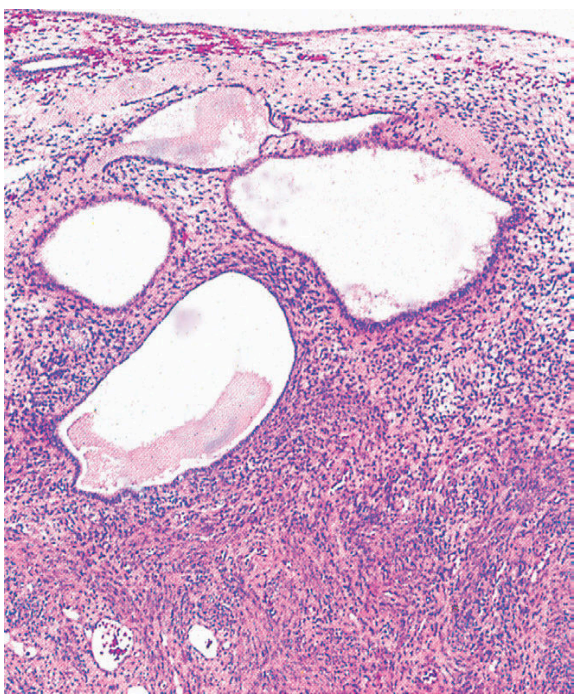


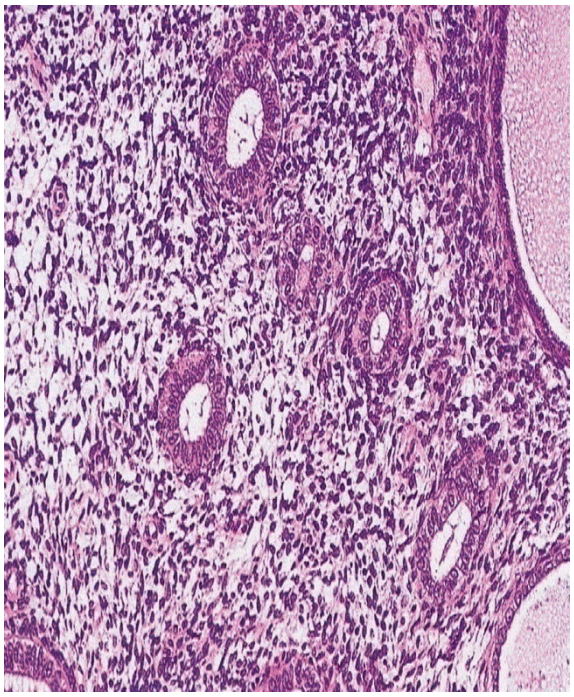


POST MENOPAUSAL

After menopause, the cyclical production of oestrogen and progesterone from the ovaries stops and the whole genital tract undergoes atrophy. As seen in the image the endometrium is thin, consisting only of the stratum basalis, and the glands are sparse and inactive. In some women, the glands become dilated to form cystic spaces .At higher magnifications ,the glandular epithelial cells are cuboidal or low columnar with no mitotic figures or secretory activity. The epithelium which lines cystically dilated glands , is often flattened. The stroma is much less cellular and no mitotic activity is present. The

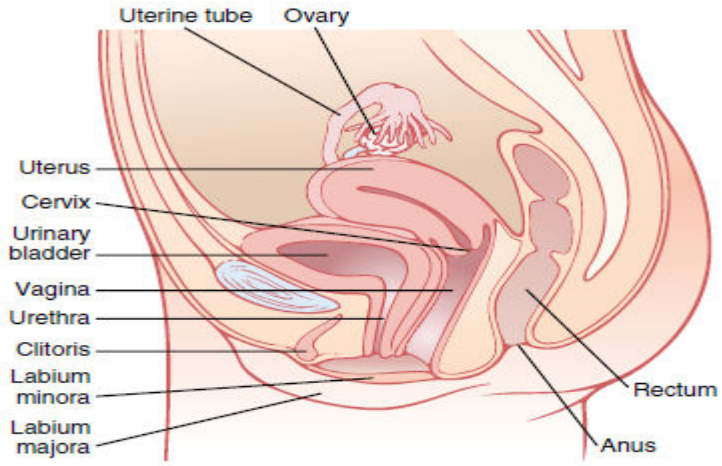
myometrium also becomes atrophic after menopause and the uterus shrinks to about half its original size.[9]

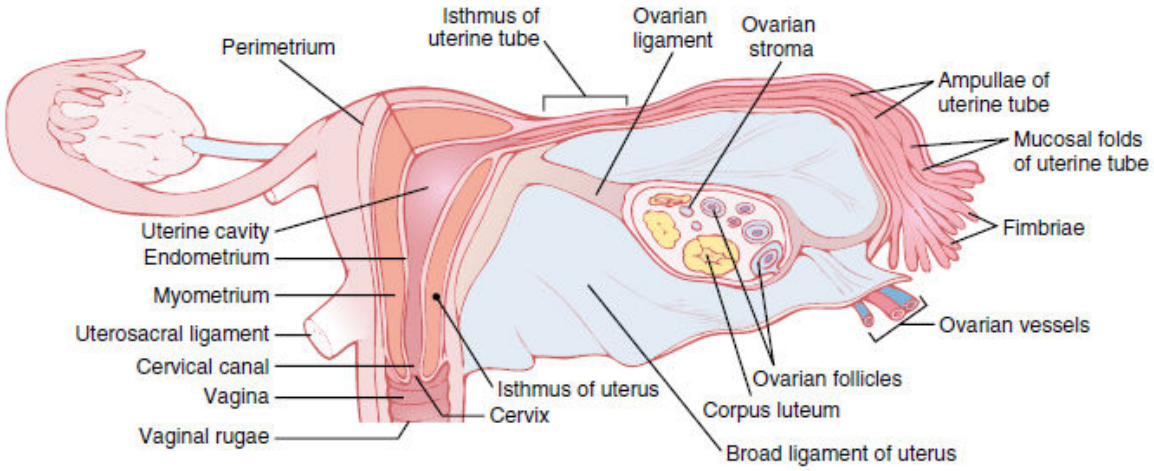




PHYSIOLOGY

The principal organs of the human female reproductive system, including the ovaries, fallopian tubes and uterus.Reproduction start with the development of ova in the ovaries. In the middle of each monthly sexual cycle ,a single ovum is expelled from an ovarian follicle into the abdominal cavity near the open fimbriated ends of the fallopian tubes. This ovum then passes through one of the fallopian tubes into the uterus, if it is fertilized by a sperm, Itgets implanted in the uterus, where it develops into a fetus, a placenta, membranes and eventually into a baby. As the female fetus develops, primordial ovadifferentiate from the germinal epithelium and migrate into the substance of the ovarian cortex. Each ovum then collects around it in a layer of spindle cells from the ovarian stroma and causes them to take on epithelioid characteristics; they are then called as granulose cells. The ovum that surrounded by a single layer of granulose cells is called a primordial follicle. The ovum at this stage is immature, requiring two more cell divisions before it can be fertilized by a sperm. At this point, the ovum is called a primary oocyte. During all the reproductive years of adult life, between about 13 and 46 years of age, 400 -500 of the primordial follicles develop to expel their ova—one each month; the remainder degenerate. At the end of reproductive age (at menopause), only a few primordial follicles remain in the ovaries and even these degenerate.[10]





FEMALE HORMONAL SYSTEM-

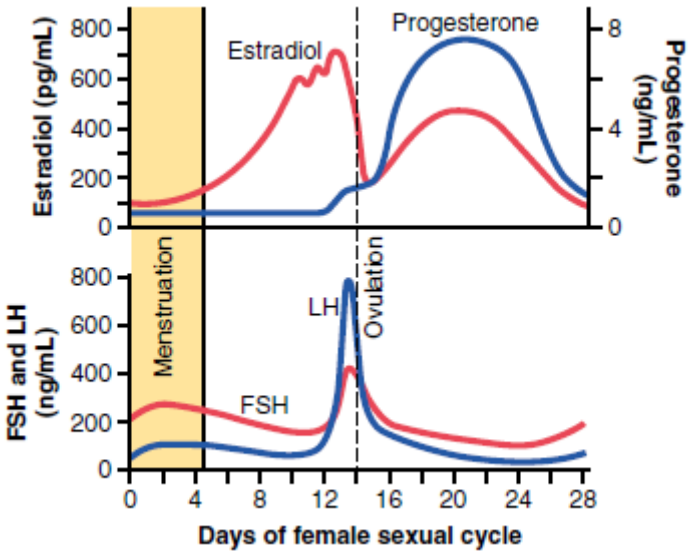
The female hormonal system, consists of three hierarchies of hormones, as follows:

1. A hypothalamic releasing hormone-gonadotropin releasing hormone(GnRH)

2. The anterior pituitary sex hormones, follicle-stimulating hormone(FSH) and luteinizing hormone (LH),both are secreted in response to the release of GnRH from the hypothalamus

3. The ovarian hormones, estrogen and progesterone, are secreted by the ovaries in response to the two female sex hormones from the anterior pituitary gland.

These various hormones are secreted during different parts of the female monthly sexual cycle. The image shows approximate change in concentrations of the anterior pituitary gonadotropic hormones FSH and LH (bottom two curves) and of the ovarian hormones estradiol and progesterone. The amount of GnRH released from the hypothalamus increases and decreases much less during the monthly cycle.[10]



Monthly Endometrial Cycle and Menstruation-

Associated with the monthly cyclical production of estrogens and progesterone by the ovaries is an endometrial cycle in the lining of the uterus that goes through the following stages: (1) proliferation of the uterine lining- endometrium; (2) development of secretory changes in the endometrium; and (3) Shedding of the endometrium, which is known as menstruation.[10]

Proliferative Phase (Estrogen) of theEndometrial Cycle that Occurs Before Ovulation.

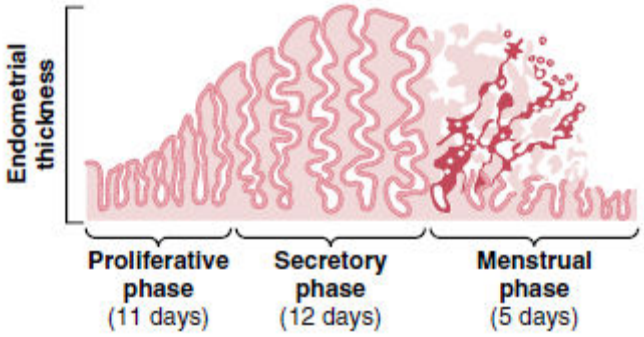
At the beginning of each monthly cycle, most of the endometrium has been shed by menstruation. After menstruation, only a thin layer of endometrial stroma remains and the

only epithelial cells that are left are those located in the remaining deeper portions of the glands and crypts of the endometrium. Under the influence of estrogens ,secreted in increasing quantities by the ovary during the first part of the monthly ovarian cycle, the stromal cells and the epithelial cells proliferate rapidly. The endometrial surface is re-epithelialized within 4 to 7 days after the beginning of menstruation. Then, during the next week and a half, before ovulation occurs, the endometrium increases greatly in thickness, owing to increasing numbers of stromal cells to progressive growth of the endometrial glands and new blood vessels into the endometrium. At the time of ovulation, the endometrium is 3 to 5 millimeters thick. The endometrial glands, especially those of the cervical region, secrete a thin, stringy mucus. The mucus strings actually align themselves along the length of the cervical canal, forming channels that help guide sperm in the proper direction from the vagina into the uterus.[10]

Secretory Phase (Progestational) of theEndometrial Cycle, Occurring After Ovulation-

During the latter half of the monthly cycle, after ovulation has happened, progesterone and estrogen together rare secreted in large quantities by the corpus luteum. The estrogens cause minimal additional cellular proliferation in the endometrium during this phase of the cycle, whereas progesterone causes marked swelling and secretory changes of the endometrium. The glands are more tortuous; an excess of secretory substances accumulates in the glandular epithelial cells. The cytoplasm of the stromal cells increases; lipid and glycogen deposits increase in the stromal cells; and the blood supply to the endometrium further increases in proportion to the developing secretory activity, with the blood vessels becoming highly tortuous. At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeters. The purpose of all these endometrial changes is to produce a highly secretory endometrium

that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a fertilized ovum. Then, once the ovum implants in the endometrium, the trophoblastic cells on the surface of the ovum (blastocyst)begins to digest the endometrium and absorb the endometrial stored substances, thus making great quantities of nutrients available to the implanting embryo.[10]



Menstruation-

If the ovum is not fertilized, the corpus luteum in the ovary suddenly involutes and the ovarian hormones (estrogens and progesterone) decrease to low levels of secretion, andmenstruation follows. Menstruation is caused by the reduction of ovarian hormones, especially progesterone, at the end of the monthly ovarian cycle. The initial effect is decreased stimulation of the endometrial cells by these hormones, rapidly followed by involution of the endometrium itself to about 65 percent of its previous thickness. Then ,during the 24 hours before the onset of menstruation, the tortuous blood vessels leads to vasospasm of the the mucosal layers of the endometrium , mostly because of, release of a vasoconstrictor material— prostaglandins that are present in abundance at this time. The vasospasm,causes decrease in nutrients to the endometrium ,and the loss of hormonal stimulation initiates necrosis in the endometrium, especially of the blood vessels. As a result of this blood first seeps into the vascular layer of the endometrium and the hemorrhagic areas grow rapidly over a period of 24 to 36 hours. Gradually, the necrotic

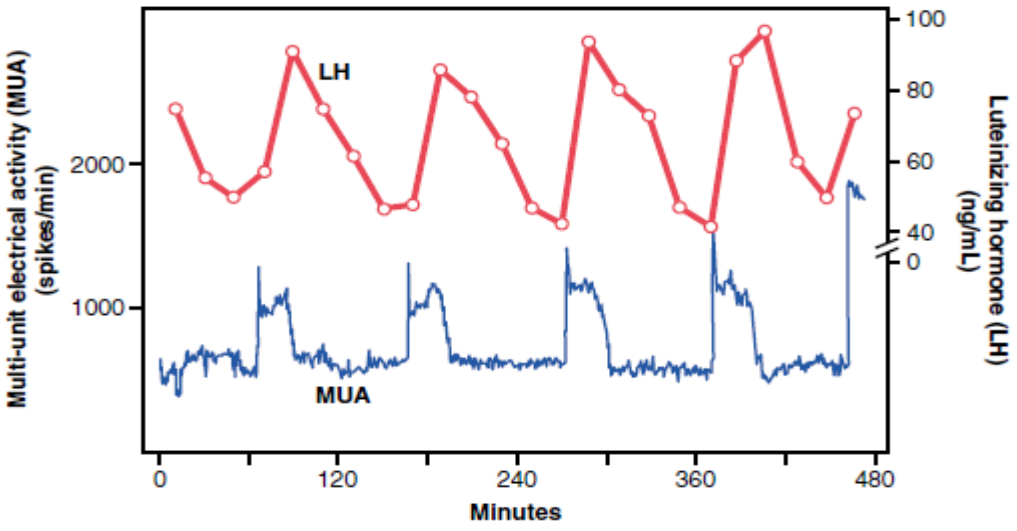
outer layers of the endometrium separates from the uterus at the sites of the hemorrhages until, about 48 hours after the onset of menstruation, all the superficial layers of the endometrium have shed. The mass of desquamated tissue and blood, along with the contractile effects of prostaglandins or other substances initiate uterine contractions that expel the uterine contents. During normal menstruation, approximately 40 milliliters of blood and an additional 35 milliliters of serous fluid are lost. The menstrual fluid normally does not clot because of a fibrinolys in that is released along with the necrotic endometrial tissue. The presence of clots during menstruation is a clinical evidence of some uterine pathology.[10]

The Hypothalamus releases GnRH,Causing the Anterior Pituitary Gland to SecreteLH and FSH.

Secretion of most of the anterior pituitary hormones is controlled by the hypothalamus and then it is transported to the anterior pituitary gland by way of the hypothalamic-hypophysial portal system.[10]

Pulsatile Release of LH from the Anterior Pituitary is caused by Intermittent, Pulsatile Secretion of GnRH by the Hypothalamus .

There is pulsatile secretion of GnRH from the hypothalamus lasting 5 to 25 minutes occuring in every 1 to 2 hours. The curve shows the electrical signals in the hypothalamus that cause pulsatile secretion of GnRH. The pulsatile release of GnRH causes intermittent secretion of LH about every 90 minutes.[10]



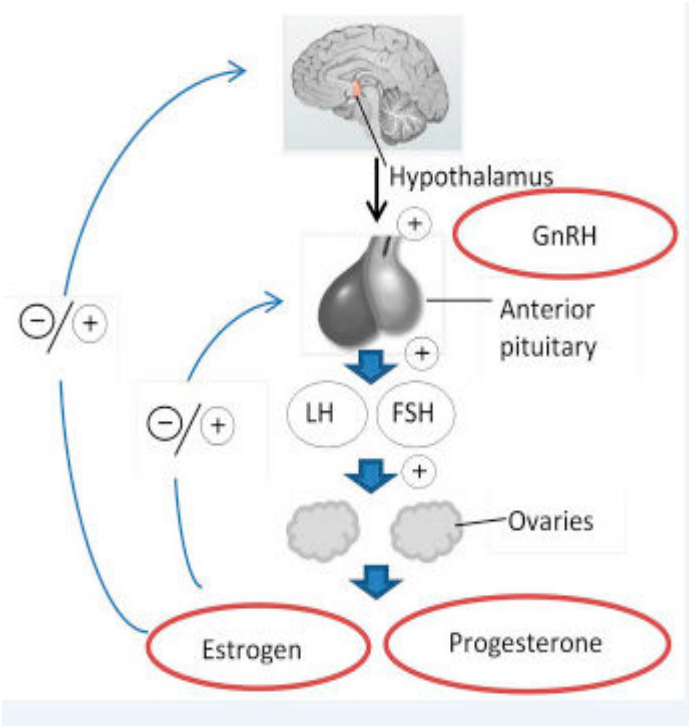
Negative Feedback Mechanism of Estrogen and Progesterone to reduce FSH and LH Secretion-

Estrogen even in small quantity causes inhibition of production of both LH and FSH.In addition to this if progesterone is available, the inhibitory effect of estrogen is increased.These feedback effect mainly operates on the anterior pituitary gland directly, but also to a lesser extent on the hypothalamus to reduce the secretion of GnRH, by changing the frequency of the GnRH pulses.[10]

In addition to the feedback effects of estrogen and progesterone, other hormones are also involved to a lesser extent, especially inhibin, which is secreted by the granulosa cells of the corpus luteum .This hormone has the same effect in the female as in the male—inhibiting the secretion of FSH and, to a lesser extent, LH by the anterior pituitary gland.[10]

Positive Feedback Effect of Estrogen Before Ovulation—The Preovulatory LH Surge.

For reasons not clear, the anterior pituitary secretes increased amounts of LH for a day or two beginning 24 to 48 hours prior to ovulation. The figure below shows a smaller preovulatory surge of FSH too. Experiments have shown that if we infuse estrogen in a female above a critical rate for 2 to 3 days during the latter part of the first half of the ovarian cycle that will cause rapid accelerating growth of the ovarian follicles, as well as rapid accelerating secretion of ovarian estrogens. During this stage, secretions of both LH and FSH by the anterior pituitary are at first is slightly suppressed. Then LH secretion increases abruptly six to eight times, and FSH increases about twice. The increased secretion of LH causes ovulation to occur .The cause of this abrupt surge in LH secretion is not known. However, there are several possible explanations: (1) It has been suggested that estrogen at this point in the cycle has a peculiar positive feedback effect of stimulating pituitary secretion of LH and, to a lesser extent, FSH; this is in sharp contrast to its normal negative feedback effect that occurs during the remainder of the female monthly cycle. (2) The granulosa cells of the follicles begin to secrete small but increasing quantities of progesterone a day or so before the preovulatory LH surge, and it has been suggested that this might be the factor that stimulates the excess LH secretion .Without this normal preovulatory surge of LH, ovulation will not occur.[10]



DEFINITIONS[10]

Menorrhagia (hypermenorrhea)- Excessive (> 80 mL) and prolonged (>7 days) bleeding occurring at regular intervals.

Polymenorrhea-Cyclic bleeding that occurs more frequently than every 21 days and persists in that frequency. If there is an associated increase in amount and duration of bleeding, it is called epimenorrhagia or polymenorrhagia.

Metrorrhagia-Cycles are irregular and can manifest as either contact bleeding or intermenstrual bleeding.

Menometrorrhagia- This term is applied when bleeding occurs erratically and excessively that the menstrual phase cannot be determined at all.

Oligomenorrhea- Cyclical bleeding that occurs at regular but long (>35 days) intervals.

Hypomennorhea- When the amount of menstrual bleeding is abnormally small and lasts for less than 2 days.

Intermenstrual bleeding-This refers to bleeding (usually not excessive) that occurs between otherwise normal menstrual cycles.

Precocious menstruation-Denotes the occurrence of menstruation before the age of 10 years.

Postcoital bleeding-Denotes vaginal bleeding after sexual intercourse.

METHODS OF ENDOMETRIAL SAMPLING-

DILATATION AND CURETTAGE (D&C)- For decades, diagnostic curettage has been the most common operation performed on women. The procedure is not without its limitations. Hemorrhage, infection, and uterine perforation may occur and, because cervical dilatation is painful, the risks associated with the necessary general anesthetic are also present.[13]

ENDOMETRIAL BIOPSY-Removal of a single strip of endometrium may be undertaken as an outpatient procedure, without cervical dilatation or general anesthetic. This technique is rarely used.[13]

VABRA ASPIRATOR-This is a suction curette device composed of a 3–4 mm diameter steel cannula that has an opening on one side of its bent tip. The endometrial tissue is obtained by suction with an attached syringe. The amount of material this procedure captures varies.[13]

PIPELLE BIOPSY-This is probably the most widely used outpatient method in the United States and Europe to sample the endometrial cavity. This procedure is quick and causes significantly less pain than Novak curette or Vabra aspirator. Although it produces less tissue, the diagnostic accuracy of the Pipelle biopsy is similar to that of the Vabra aspirator. It is no less reliable than other techniques for identifying endometrial carcinoma, although some studies have suggested a poor pick-up rate for early, low-volume tumors.(13)

ENDOMETRIAL RESECTION-Transcervical resection of the endometrium is one of the different methods used for endometrial ablation. It is used as a conservative management of abnormal uterine bleeding. It should be done only after excluding hyperplasia and carcinoma by other methods of sampling like hysteroscopic biopsy or D&C. The endometrium should be suppressed hormonally before doing this procedure. The tissue obtained is composed mainly of myometrial tissue. However, adenomyosis cannot be reliably diagnosed by this procedure.(14)

ADEQUACY OF SPECIMEN-A scant specimen is a problem encountered frequently by pathologists because of the widespread use of techniques like pipelle biopsy. An adequate sample is widely obtained in late proliferative, late secretory, hyperplasias and carcinomas. A scant specimen is commonly seen in postmenopausal atrophy. Nevertheless, a scant specimen cannot rule out hyperplasia or carcinoma as cases have been reported in which biopsy has been scanty while subsequent hysterectomy has revealed carcinoma.It is not necessary to repeat the biopsy when a scant tissue is noted. The specimen can be deemed as adequate even when a small amount of endometrial tissue is found. It is advisable to use the term unassessable rather than inadequate when a scant tissue is seen. McCluggage classified endometrial specimens into “inadequate” (no tissue is obtained) and “unassessable” (scant tissue is present). This classification holds

little significance as the final clinical diagnosis between the two categories doesn't differ significantly.[15] The findings of other investigations like ultrasound and hysteroscopy should be taken into account before going for repeat biopsy in such cases. If the clinical features and other investigations point to some pathology, then D&C should be done.[5]

CAUSES OF AUB-

The term Dysfunctional uterine bleeding was previously used to denote heavy menstrual bleeding without any organic cause. The term Abnormal Uterine Bleeding was introduced by FIGO in 2011 to include all abnormal uterine bleeding with or without any organic lesion. The newer classification system is known by the acronym **PALM–COEIN.**[16]

CLASSIFICATION OF AUB-Contrary to the PALM group, the COEIN group cannot be detected by imaging and histopathology.

CLASSIFICATION OF AUB (FIGO- 2011)			
Structural causes (PALM)		**Non structural systemic causes (COEIN)**	
Polyp	AUB-P	Coagulopathy	AUB-C
Adenomyosis	AUB-A	Ovulatory dysfunction	AUB-O
Leiomyoma - Submucosal myoma - Other myoma	AUB-L AUB-L SM AUB-LO	Endometrial	AUB-E
Malignancy and hyperplasia	AUB-M	Iatrogenic	AUB-I
		Not yet identified	AUB-N

Polyp (AUB-P)- Polyps can be detected by ultrasound, hysteroscopy or histopathology. They can be subdivided on the basis of number, size, location and histology.[17]

Adenomyosis (AUB-A)- It can be diagnosed by ultrasound or MRI. It is further subdivided on the basis of the depth of myometrial invasion. Most often, it is asymptomatic and an incidental finding in hysterectomy specimens.[17]

Leiomyoma (AUB-L)- Leiomyomas usually are not the cause of abnormal uterine bleeding. Mostly they are incidental findings. Myomas that are causal in abnormal bleeding usually involve the uterine cavity. They are further subdivided into primary, secondary and tertiary groups based on their number, size and location.[17]

Malignancy and pre-malignant lesions-It is rare in reproductive age group. In this age group, it occurs usually in the setting of polycystic ovarian disease and chronic anovulation. Diagnosis is made by histopathological examination of the endometrium (D/C, biopsy).[17]

Coagulopathy (AUB-C)- Coagulopathies are the cause of AUB in 13 to 20 % of women in the reproductive age group. The most common cause is Von Willebrand's disease.[19]

Ovulatory disorders (AUB-O)- Ovulatory disorders are the cause of AUB in 20% of cases. These are the result of "Luteal – out – of – phase" events (LOOP) with deficient progesterone. Hypothyroidism and hyperprolactinemia are other causes.[19]

Endometrial causes (AUB-E)- Endometrium normally produces prostaglandins from arachidonic acid, which is a fatty acid. Of these, PGE2 and PGI2 are vasodilators and antiplatelet aggregates. PGF2a and thromboxane A2 cause vasoconstriction and platelet aggregates. Progesterone is responsible for the secretion of PGF2a. In anovulatory cycles,

the absence of progesterone and thereby of PGF2a causes menorrhagia. Rare endometrial causes of AUB include tuberculous endometritis and infection, especially chlamydia.[19]

Iatrogenic (AUB-I)- It is caused by steroidal hormones administered as oral contraceptives or IUCD. Copper T may cause "break-through bleeding" or menorrhagia. Other drugs causing abnormal bleeding include anticoagulants, phenothiazines and tricyclic antidepressants.[19]

Not- classified (AUB-N)- This includes rare causes like arteriovenous malformations, varicose veins of uterine vessels, myohyperplasia and cases for which no cause can be identified by routine investigations.[19]

AUB CAN BE ACUTE OR CHRONIC-

Acute bleeding- may occur sporadically (de novo) or may be superimposed on chronic AUB, and requires immediate treatment.[18]

Chronic AUB - Abnormal menstrual bleeding related to volume, timing, regularity and duration of bleeding that lasts for 6 months (minimum 3 months), and requires thorough investigations.[18]

DYSFUNCTIONAL UTERINE BLEEDING-The term Dysfunctional Uterine Bleeding is used once the organic causes of abnormal bleeding has been excluded. Upto 50% of women with abnormal bleeding have DUB [18] . DUB can be classified into

1. Ovulatory – 10 to 20%
2. Anovulatory – 80 to 90%.

OVULATORY BLEEDING-Ovulatory bleeding can present as either polymenorrhea or menorrhagia.

Polymenorrhea

It usually occurs following childbirth and abortion, during adolescence and premenopausal period, and in pelvic inflammatory disease. This is due to shortening of follicular phase due to hyperstimulation by FSH or premature lysis of the corpus luteum. Endometrial study prior to or within few hours of menstruation reveals secretory changes.[22]

Menorrhagia-Two types are seen

Irregular shedding of the endometrium-This is due to incomplete and slow degeneration of the corpus luteum (Halban's disease). Endometrial sampling performed after 5th or 6th day of the onset of menstruation reveals a mixture of secretory and proliferative endometrium.[22]

Irregular ripening of the endometrium-This is due to the poor formation and function of the corpus luteum. Endometrial study prior to or soon after spotting reveals patchy areas of secretory changes amidst proliferative endometrium.[22]

ANOVULATORY UTERINE BLEEDING-

Continued exposure to estrogen in the presence of anovulation leads to marked endometrial proliferation. After a certain extent, the endometrium cannot support the proliferation and shedding occurs called as "anovulatory shedding". This should be differentiated from the normal menstrual shedding. The absence of secretory exhaustion and presence of fibrin clots distinguishes anovulatory shedding from menstrual endometrium. Also in anovulation the glands lose their uniformity in size, shape and distribution leading to a pattern called disordered proliferative endometrium. It also leads to cystic dilatation of the glands and tubal metaplasia.[19] The underlying cause is unknown. Presumably, the failure of ovulation reflects an abnormal gonadotrophin stimulus.[20]

Metropathia Haemorrhagica-It is a specialized form of anovulatory AUB, seen in women between 40 and 45 years. The basic fault may lie in the ovaries or may be due to a disturbance of the rhythmic secretion of the gonadotropins. There is a slow increase in the secretion of estrogen but no negative feedback inhibition of FSH. The net effect is a gradual rise in the level of estrogen with a concomitant phase of amenorrhea for about 6–8 weeks. After a variable period, however, the estrogen level falls resulting in the endometrial shedding with heavy bleeding. Histopathology shows thick endometrium with polypoidal projections. There is cystic glandular hyperplasia. Some of the glands are small, others are large giving the appearance of "Swiss cheese" pattern.[21]

SPECIFIC CAUSES OF ABNORMAL UTERINE BLEEDING-

ENDOMETRITIS -Endometritis commonly occurs in the reproductive age group. It usually presents with abnormal uterine bleeding. Predisposing factors include recent pregnancy, prior instrumentation, intrauterine devices and cervical stenosis. Endometritis

may also coexist with polyps, fibroid, hyperplasia or endometrial carcinoma. The endometrium shows proliferative activity and glandular architectural distortion. There is surface breakdown similar to that seen in menstrual breakdown. In low power, the stromal cells show spindle appearance.[23]

In acute endometritis, the predominant inflammatory cells are neutrophils, sometimes seen within the glandular lumina forming microabscesses. The characteristic finding of endometritis is the presence of plasma cells. Other inflammatory cells like neutrophils and lymphocytes can be present in normal endometrium. In chronic endometritis, lymphocytes are prominent sometimes forming lymphoid follicles.[24] Endometrial surface and glandular epithelium may show metaplastic changes. Immunohistochemistry using VS38 or Syndecan can be used to differentiate plasma cells from the endometrial stromal cells, which resembles plasma cells. Plasma cells show positivity to both the markers whereas stromal cells positive for only VS38.[26]

EFFECTS OF EXOGENOUS HORMONAL AGENTS AND DRUGS-A wide variety of hormonal agents are used in women for various indications. The effects of the most common hormonal agents used are discussed below.[25]

ESTROGEN ONLY HORMONE REPLACEMENT THERAPY

These are rarely used in women because of the risk of endometrial hyperplasia and adenocarcinoma. The morphological features include proliferative activity similar to disordered proliferation, endometrial hyperplasia or endometrioid adenocarcinoma.[33] The risk of carcinoma increases with the dose and length of treatment and the adenocarcinoma which develops is usually of an early stage and low grade.[25]

COMBINED ESTROGEN AND PROGESTIN HORMONE THERAPY

Combined therapy is preferred in women with uterus due to the disadvantages of estrogen only therapy.[5] Estrogen and progestin combination may be given sequentially or simultaneously (continuously). In sequential therapy, the endometrium shows weakly proliferative activity during estrogen therapy and poorly develop secretory activity during progestin therapy. This regimen doesn't completely abolish the risk of carcinoma and the risk of endometrial hyperplasia with sequential regimen is 5.4%. With continuous combined regimen, the endometrium shows atrophy or weak secretory activity.[27]

This regimen reduces the risk of development of endometrial hyperplasia and carcinoma. Hence continuous combined regimen is preferred to sequential HRT in perimenopausal women and postmenopausal women.[29]

PROGESTIN – ONLY COMPOUNDS-These are commonly prescribed for abnormal uterine bleeding, endometriosis, contraception and for endometrial protection in patients taking tamoxifen. They usually result in endometrial atrophy with predecidual changes or decidualisation of the stroma.[30]

GONADOTROPHIN RELEASING HORMONE AGONISTS-These are usually used in the management of uterine fibroids and endometriosis. The continuous administration of GnRH agonists results in decreased production of FSH and LH thereby causing decreased production of estrogen by the ovaries.[28] This results in shrinkage of uterine leiomyomas. The endometrium shows atrophy or weak proliferative activity.[35]

ANDROGENS-These are used in the treatment of endometriosis, as HRT, menorrhagia and endometrial hyperplasia.[31] The endometrium has weak secretory activity during the initial phase of treatment but with continued treatment, the endometrium shows atrophic changes.[32]

TAMOXIFEN-

It is used in the prevention and treatment of breast cancer. In the breast, it acts as an estrogen antagonist, whereas in the endometrium it acts as a weak estrogen agonist. Tamoxifen is associated with a variety of benign and malignant lesions in the endometrium. Patients receiving treatment for longer duration and at higher doses are particularly at high risk. Benign lesions include polyps and hyperplasia. Tamoxifen associated polyps are larger in size. Malignant lesions seen with tamoxifen usage are endometrial adenocarcinoma, including both endometrioid and serous types and carcinosarcomas.[34]

ENDOMETRIAL EPITHELIAL METAPLASIA

Metaplasias are alterations in which the normal endometrial epithelium is substituted by a different epithelium.[11] Metaplasias are commonly associated with endometrial polyps, exogenous hormone therapy, intrauterine devices, chronic endometritis and pyometra.[37] Endometrial metaplasias tend to be associated with epithelial hyperplasias or endometrial adenocarcinomas, but by themselves are non-neoplastic. WHO classification subdivides endometrial metaplasia into mucinous, squamous, ciliary, hobnail, eosinophilic, clear cell, surface syncytial, papillary proliferation, and Arias–Stella effect.[20] Squamous and mucinous metaplasias are particularly common with endometrioid adenocarcinoma.The clear cell and papillary syncytial metaplasias must be differentiated from type 2 endometrial cancers or serous endometrial intraepithelial carcinomas.[36] In serous EIC and serous endometrial cancers, immunohistochemistry reveals strong p53 immunoreactivity while ER is generally negative, whereas the majority of epithelial metaplasias show weak p53 immunoreactivity and strong positivity for ER.

ENDOMETRIAL POLYPS

These are the cause of uterine bleeding in 2 to 23% of patients undergoing endometrial biopsy. [21] Polyps can occur at any age, but are most commonly seen in the perimenopausal age group. Polyps represent circumscribed foci of hyperplasia of the endometrium secondary to hormonal stimulus. Hormone replacement therapy and tamoxifen are associated with an increased occurrence of polyps. More often the glands and stroma of polyps are non-functional and doesn't respond to hormonal stimulus. Hence, they do not show the cyclical changes seen in normal endometrium. Grossly, polyps may be single or multiple, sessile or broad based, pedunculated or attached to the endometrium by a slender stalk. The histological features of the polyps include the following

1. Polypoid pieces of tissue lined by epithelium on 3 sides
2. Stroma altered by fibrosis or excessive collagen
3. Glands are distended with crowding
4. Glands out of phase with the adjacent non-polypoidal endometrium ie. In a different phase compared with the adjacent endometrium
5. Blood vessels in the stroma have a thick wall.[38-41]

Polyps associated with tamoxifen use are characteristically multiple, large and fibrotic and exhibit stromal decidualisation and mucinous metaplasia [22].

The differential diagnosis for polyps includes endometrial hyperplasia, endometritis, adenosarcoma and adenofibroma. The distinction with endometrial hyperplasia is made by examining the stroma. In hyperplasia, the stromal cells are active with large vesicular nuclei and occasional mitotic figures, whereas the stroma of a polyp is composed of spindle (fibroblast-like) cells and contains abundant extracellular connective tissue and

large, thick-walled blood vessels. Malignant transformation of endometrial polyps is rarely encountered. They can present as either in-situ or invasive serous carcinomas [23].

ENDOMETRIAL HYPERPLASIA

Definition and classification-Hyperplasia is characterised by the multiplication of endometrial glands of various sizes and shapes which results in higher glandular to stromal ratio. There are many classification systems for endometrial hyperplasia. But only the Kurman and Norris classification system is commonly used and currently approved by the World Health Organization (WHO) [24]. It takes into account both architectural and cytological features. It is classified into *simple* and *complex* based on architecture and into *typical* and *atypical* based on the cytology.

Kurman and Norris (1986) classification of endometrial hyperplasia-

Hyperplasia

- Simple
- Complex

Atypical hyperplasia

- Simple
- Complex

WHO classification of endometrial hyperplasia

Hyperplasia without atypia

- Simple hyperplasia without atypia
- Complex hyperplasia without atypia

Atypical hyperplasia

- Simple atypical hyperplasia (very rare)
- Complex atypical hyperplasia

Clinical features-

Endometrial hyperplasias are most commonly seen in the perimenopausal period. It also can be encountered in women in the reproductive age group. Hyperplasia develops as a result of unopposed estrogenic stimulation.[42] The etiologies for hyperplasia include

1. Prolonged anovulation
2. Estrogen only Hormone Replacement Therapy
3. Obesity
4. Polycystic ovarian disease (Stein–Leventhal syndrome)
5. Granulosa and theca cell tumors of the ovary

All these causes have in common unimpeded estrogen stimulation.

Hyperplasias can also occur in postmenopausal woman.[45] Endometrial atrophy is the most frequent etiology of AUB in this group of women. In one study of postmenopausal bleeding, atrophy was the commonest finding followed by hyperplasia and endometrial cancer [25].

Gross features-

Gross pathological findings are non-specific. Usually the volume of curettings is large in hyperplasias. The color is white to tan. It may be seen as diffuse thickening or as localised projections into the endometrium, which sometimes mimics a polyp.[44]

HYPERPLASIA WITHOUT ATYPIA

SIMPLE HYPERPLASIA

It resembles mid to late proliferative endometrium. The endometrial glands vary in size and shape. Some glands show cystic dilatations giving the appearance of "swiss-cheese" pattern. This is referred to in older classification as cystoglandular hypertrophy. But not all cystic glands are hypertrophied. Some cystic glands show atrophy which is called cystic endometrial atrophy [7]. The stroma is abundant. The epithelial lining is pseudostratified, the nuclei are elongated, chromatin is dispersed and nucleoli are less prominent. The epithelial lining shows little budding.[43]

COMPLEX HYPERPLASIA

In complex hyperplasia, the glands are densely packed with back to back arrangement. The glandular structures are increased in relation to the stroma, which is decreased. The glands show more structural complexity with more branching in the form of outfoldings and inpouchings. Cytologically the glandular epithelial cells are identical to that of simple hyperplasia.[59,60]

ATYPICAL HYPERPLASIA

The presence of atypical nuclei is an important finding due to the risk of development of carcinoma. Atypical nuclei are rounded, pleomorphic, show stratification with loss of polarity and have condensed chromatin with prominent nucleoli giving a vesicular appearance. Atypia may not be seen in all glandular epithelial cells. Occasional atypical cells can be ignored. Metaplastic changes are often found in association with atypical hyperplasia. The presence of histiocytes in the stroma gives a clue to diagnose hyperplasia in asymptomatic postmenopausal women.[48]

ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA (EIN)

EIN comes under a different type of classification system of hyperplasia. It is a premalignant lesion for endometrial carcinoma. It is diagnosed on the basis of clinical, histomorphometric, molecular and genetic factors. EIN represents monoclonal proliferation of cells with growth advantage conferred by mutations.

These cells are able to grow without hormonal support. Although EIN cannot be equated with a single diagnosis in WHO classification, it mostly corresponds to complex atypical hyperplasia followed by complex hyperplasia.[50]

Differential diagnosis

These includes disordered proliferative phase, tubal metaplasia, polyps, cystic atrophy and endometrial breakdown. Atypical hyperplasia should be differentiated from well differentiated adenocarcinoma and atypical polypoid adenomyoma. Distinction between atypical hyperplasia and adenocarcinoma is made out by looking for the stromal invasion which is present in the latter.[46]

Behaviour

Hyperplasia without atypia usually regress. Atypical hyperplasia is associated with a high risk of developing adenocarcinoma. In one study, 23% of atypical hyperplasia progressed to carcinoma whereas in the absence of atypia the risk of progression to carcinoma decreases to 2% atypia [26]. If adenocarcinoma develops from atypical hyperplasia, it is usually well differentiated and focal with little invasion of the myometrium. It is important to note that adenocarcinoma may be co-existant with CAH (25%) (found on hysterectomy) or may evolve from hyperplasia (30%). Age of the patient is also an

important factor influencing the behaviour of hyperplasia. Most of the simple hyperplasia in young women regress.[47]

Relationship with carcinoma

1. Most cases of endometrial carcinoma of the endometrioid type are preceded by a stage of hyperplasia.

2. Overall, relatively few patients with hyperplasia will subsequently develop cancer. Rather, the majority of the cases are responsive to progestin treatment.

3. The more severe the hyperplasia, the more likely it is to be followed by (or to be concurrent with) carcinoma.[51-53]

MANAGEMENT OF HYPERPLASIA

The factors which determine the treatment of endometrial hyperplasia include the age of the patient, the histologic type and fitness for surgery (especially in postmenopausal women).[56]

PREMENOPAUSAL WOMEN

Distinguishing between CAH and endometrial adenocarcinoma is very important especially in premenopausal women who wish to retain their fertility. Premenopausal women with abnormal bleeding should be considered for endometrial biopsy only if they have risk factors like polycystic ovarian disease or obesity as there is a low risk of having carcinoma in this age group. Hyperplasia without atypia can be treated conservatively with cyclical progestin. They should be followed up after 6 months with endometrial sampling to look for regression [26]. Women with atypical hyperplasia can be treated with progestin suppression if they wish to retain their fertility. However, they should have close follow-up with periodic endometrial samplings. Conservative management can also

be offered to women with well differentiated carcinoma. Hormonal therapy with progestin for 9 months resulted in the regression of lesions in 75% of women with carcinoma [27].

PERIMENOPAUSAL WOMEN (40 – 55 YEARS)

These women should be considered for an endometrial biopsy even though there is also at low risk of developing carcinoma. Women with atypical hyperplasia in this age group should be started on hormonal therapy with progestins. However, they should be followed up with endometrial biopsies every 3 months. Hysterectomy should be performed when hyperplasia persists in follow-up biopsy.[23]

POST MENOPAUSAL WOMEN (OVER 55 YRS OF AGE)

Women in this age group have a significantly higher risk of developing adenocarcinoma or atypical hyperplasia. Endometrial biopsy should be performed followed by fractional curettage if hyperplasia is present. If hyperplasia without atypia is detected on curettage, conservative management includes observation only or treatment with progestin. Repeated episodes of irregular bleeding unresponsive to hormonal treatment requires hysterectomy. If atypical hyperplasia is detected, hysterectomy is the management of choice. In women unfit for surgery, continuous treatment with progesterone acetate can be used to avoid surgery. For postmenopausal women on exogenous estrogens who show hyperplasia on biopsy, termination of treatment is usually sufficient to cause regression. Alternatively, a cyclical or continuous administration of medroxyprogesterone can be considered to reduce the risk of carcinoma.[25]

ENDOMETRIAL INTRAEPITHELIAL CARCINOMA (EIC)

EIC is the precursor of serous endometrial carcinoma. It is an intraepithelial malignancy with focal or diffuse involvement of the surface and glandular epithelium. The nuclei are hobnail shaped and show marked atypia. Sometimes they are associated with metastatis, especially to peritoneal surfaces. Hence they are not in situ carcinomas. The presence of disseminated disease is an important prognostic factor. So Wheeler et al combine EIC with serous carcinoma measuring < 1 cm and gave the terminology "minimal uterine serous carcinoma" [28] . They can be differentiated from serous carcinoma by the absence of stromal invasion. It usually occurs in the setting of endometrial atrophy seen in older, postmenopausal women. EIC is often present on the surface of a polyp. Immunohistochemistry shows intense reactivity for p53.[66]

Behaviour

EIC commonly coexists with invasive carcinoma, usually serous type. EIC or serous carcinoma without evidence of metastasis has a very good prognosis. The presence of evidence of extrauterine disease implies a bad prognosis. Hence, it is important to do a thorough staging at the time of hysterectomy when a diagnosis of EIC is made by biopsy.[64]

CARCINOMA OF THE ENDOMETRIUM

Endometrial carcinoma has emerged as the commonest gynaecologic malignancy in developed countries. This is because of the increased incidence of risk factors like obesity and longer survival of women [29]. However, in developing countries cervical cancer continues to be the commonest malignancy of the genital tract. Endometrial carcinoma usually presents in the early stages with abnormal vaginal bleeding. Hence they are

amenable to curative therapy by hysterectomy. It is mainly a disease of postmenopausal women.[71]

ENDOMETRIAL ADENOCARCINOMA, ENDOMETRIOID TYPE (TYPE I)

These are the most common type of endometrial cancers accounting for about 80% of cases. They usually occur in 55- 65 years of age, slightly younger than type II cancers. They usually occur in association with the estrogen related risk factors described below [30]. The precursor lesion is atypical hyperplasia or endometrial intraepithelial neoplasia. These tumors are usually of low grade. They are less invasive and have less propensity for lymphatic spread. The prognosis is generally good. The genetic alterations include PTEN mutations, microsatellite instability and K-ras mutation.[65]

ENDOMETRIAL ADENOCARCINOMA, NON-ENDOMETRIOID TYPE (TYPE II)

Non-endometrioid tumors occur in older, postmenopausal women, and account for 10–20% of endometrial carcinomas. They are not associated with clinical evidence of estrogen stimulation, and usually arise from atrophic endometrium. These tumors include serous carcinoma, clear cell carcinoma and other histologic subtypes. They are usually poorly differentiated (grade 3) tumors. They arise frequently in the setting of endometrial polyps. They have rapid courses, a high degree of nuclear pleomorphism and frequent aneuploid DNA content. These tumors are aggressive with deeper myometrial invasion and increased risk of lymphatic dissemination. The prognosis is generally poor. Mutations in the tumor suppressor TP53 are present in at least 90% of serous endometrial carcinoma.[69]

A modified version of the recent World Health Organization (WHO) and International Society of Gynecological Pathologists (ISGYP) classification of endometrial carcinoma is shown below.

CLASSIFICATION OF ENDOMETRIAL CARCINOMA

1. Endometrioid adenocarcinoma
2. Serous carcinoma
3. Clear cell carcinoma
4. Mucinous carcinoma
5. Villoglandular
6. Secretory
7. Ciliated cell
8. Endometrioid adenocarcinoma with squamous differentiation
9. Squamous carcinoma
10. Mixed types of carcinoma
11. Undifferentiated carcinoma

RISK FACTORS FOR ENDOMETRIAL CARCINOMA

ESTROGENS

Estrogens are an important stimulus for the development of endometrial hyperplasia and adenocarcinoma. The widespread use of estrogens in HRT for peri and post menopausal women has resulted in a sudden rise in the incidence of endometrial cancers. The risk of developing endometrial cancer is elevated three- to sixfold in women taking unopposed estrogens [31], rising to 9.5-fold if unopposed estrogen has been used for 10 years or longer

[32]. .The increase risk can be alleviated by the addition of progestins for 7 to 10 days a month in women taking estrogen for HRT.

TAMOXIFEN

Tamoxifen is a selective estrogen receptor modulator used as adjuvant therapy for breast cancer. In women of child-bearing age, it antagonises estrogens, whereas in post-menopausal women, it has a weak estrogenic effect. Tamoxifen administration is associated with an overall slightly increased risk (two to three times) of endometrial adenocarcinoma [33].

POLYCYSTIC OVARY SYNDROME (PCOS)

PCOS is characterised by atleast two of the following features: anovulation or infrequent ovulation, androgen excess, and polycystic ovaries. The patients are usually infertile, have elevated estrogen levels, and associated insulin resistance may cause type 2 diabetes. Endometrial carcinoma occurs in less than 5% of those women with polycystic ovaries [34]

OBESITY

It is a significant risk factor for the development of endometrial cancer. The increase risk may be due to increased peripheral conversion of androgens to estrogens (estrone and estradiol) in adipose tissue and decreased levels of serum sex hormone binding globulin (SHBG).[67]

SEX CORD-STROMAL TUMORS

Granulosa cell tumors and thecoma are associated with a prolonged, excessive and unopposed estrogen production. This produces endometrial hyperplasia, EIN and

endometrial carcinoma. 9–13% of women with granulosa cell tumors develop endometrial carcinomas [35]

NON-NEOPLASTIC OVARAIN LESIONS

Endometrial carcinoma is found in over one-third of women with diffuse hyperthecosis.[65]

REPRODUCTIVE FACTORS

Nulliparity is a strong risk factor for endometrial carcinoma. Infertility, particularly when it is coupled with anovulation and progesterone deficiency is also a risk factor for development of endometrial adenocarcinoma. Early menarche, late menopause and low parity are factors associated with increased overall lifetime estrogen exposure.[69]

SYNDROMES

Endometrial carcinoma can rarely be a manifestation of hereditary cancer

Clinical features syndromes like Hereditary Non-polyposis Colonic Cancer syndrome (HNPCC or Lynch syndrome) and Cowden syndrome.

The use of oral contraceptives reduces the risk of endometrial cancer in some studies by half [36]. Cigarette smoking reduces the risk of endometrial carcinoma.[12]

The peak incidence of endometrial carcinoma is in postmenopausal women between 55 - 65 yrs of age. Carcinoma of the endometrium is rare in women under the age of 40. It usually presents with irregular or post menopausal vaginal bleeding.[68]

Gross features

The tumor may be seen as diffuse endometrial thickening or commonly as one or more multiple exophytic growths with a shaggy appearance. Sometimes it may be a polypoidal

growth. Myometrial invasion is accompanied by enlargement of the uterus. The cervix is involved in approximately 20% of cases.[70]

Microscopic features

Endometrioid carcinoma demonstrates a glandular pattern resembling normal proliferative endometrium. The grading is based on the microscopic appearance of the amount of solid growth of the glandular component. The cells are larger than cells of normal endometrium, show varying degrees of pleomorphism and prominent nucleoli. The nuclear grade is determined by the degree of anisonucleosis, chromatin distribution and size of the nucleoli. Assessment of myometrial invasion is important for staging the tumor. In the majority of cases myometrial invasion is accompanied by a desmoplastic stroma and inflammatory response. Whereas, some low grade tumors infiltrate the myometrium without stromal response.[70]

The most recent revision of the FIGO (International Federation of Gynecology and Obstetrics) Staging System is given below. Grading of the tumor should be done (both architectural and nuclear grading) before classifying endometrial carcinoma using FIGO staging.

International Federation of Gynaecology and Obstetrics Staging of Endometrial Cancer, 2009 (5)

IA	G123	Tumor limited to the inner half of myometrium
IB	G123	Tumor invasion into the outer half of myometrium
II	G123	Tumor invades cervical stroma
IIIA	G123	Tumor invades serosa and/or adnexa
IIIB	G123	Vaginal and/or parametrial involvement
IIIC1	G123	Metastases to pelvic lymph nodes
IIIC2	G123	Metastases to paraaortic lymph nodes
IVA	G123	Tumor invasion of bladder and/or bowel mucosa
IVB	G123	Distant metastases including intraabdominal and/or inguinal lymph nodes

MATERIALS AND METHODS

All the specimens of endometrial hyperplasia lesions from patients admitted to KLE'S DR. PRABHAKAR KORE HOSPITAL received in the department of pathology from January 2019 to December 2020 were considered for this study.

For retrospective cases data as well as tissue blocks were retrieved from storage.

INLUSION CRITERIA-

1.Women of peri and post menopausal age group with abnormal uterine bleeding.

2.Women who are clinically and anaesthetically stable for D&C procedure

EXCLUSION CRITERIA-

1.Clinically unstable patients.

2. Patients on anticoagulant therapy.

3.Previous 2 or more LSCS scar.

The clinical data required was collected from medical records after obtaining permission from the concerned authorities. The entire study was carried after getting the clearance from Institutional Ethics Committee.

The routine H&E staining was done using the regular protocol followed in the Department of Pathology,JNMC ,KLE Hospital.

RESULTS

Table 1: Distribution of study population based on their Age Ranges

Serial No	Age Ranges	No of Patients	Percentage (%)
1	35 to 40 years	20	40.0
2	41 to 50 years	20	40.0
3	51 to 60 years	5	10.0
4	61 to 70 years	4	8.0
5	More than 70 years	1	2.0
	Total	50	100.0

Graph 1: Distribution of study population based on their Age Ranges

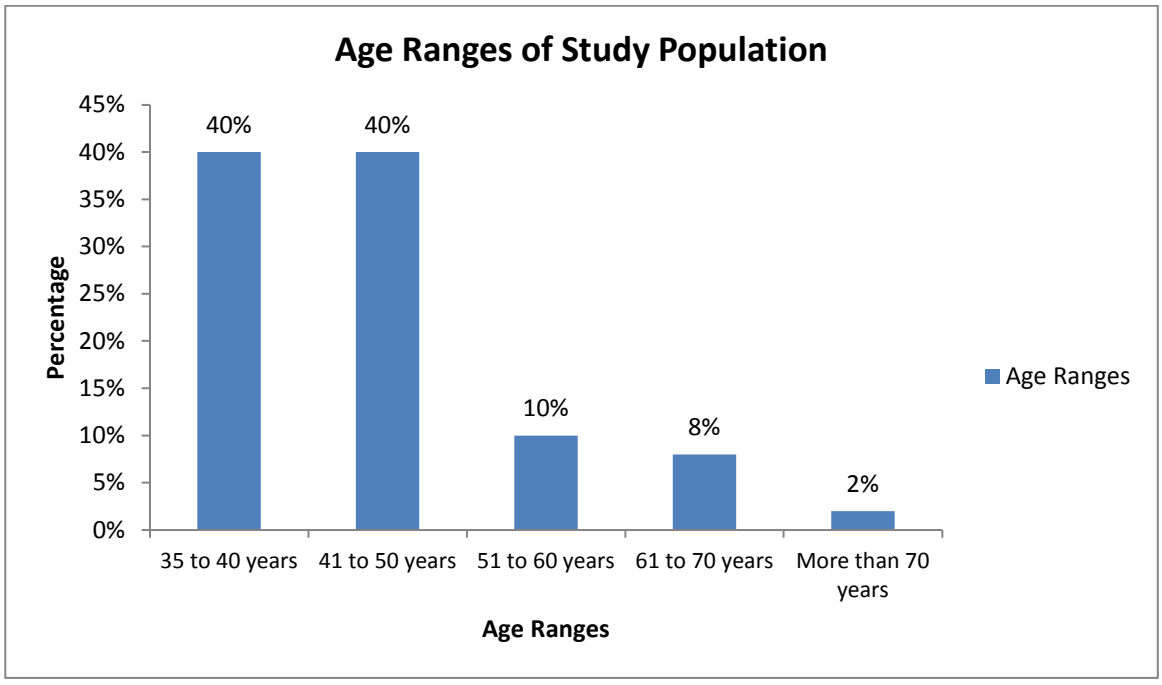


Table 1 and Graph 1, represents Age ranges of the study population. It was observed that 21 patients (42%) were less than 40 years of age, 20 patients (40%) were 41 to 50 years of age, 4 patients (8%) were 51 to 60 years of age, 4 patients (8%) were 61 to 70 years of age and 1 patient (2%) was above 70 years of age respectively.

Table 2: Distribution of study population based on their types of Parity

Serial No	Type of Parity	No of Patients	Percentage (%)
1	Grand Multipara (>4)	2	4.0
2	Multipara (2-3)	36	72.0
3	Nullipara	2	4.0
4	Primipara (1)	10	20.0
	Total	50	100.0

Graph 2: Distribution of study population based on their type of Parity

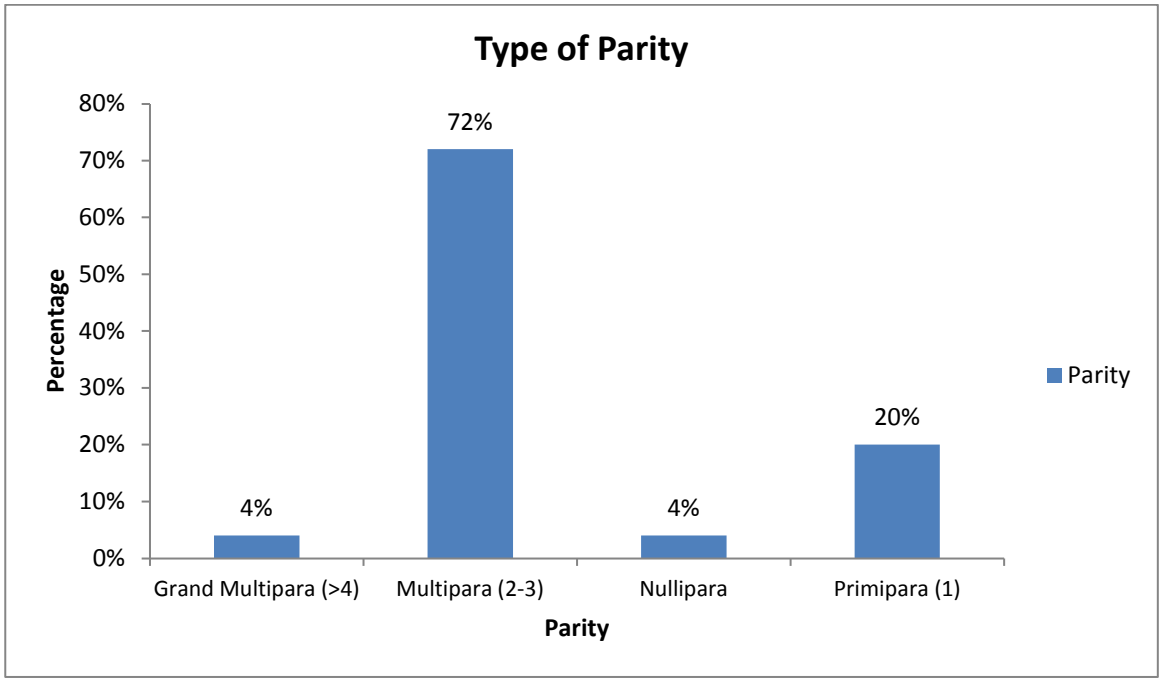


Table 2 and Graph 2 represent the type of parity in the study population. It was observed that 2 patients (4%) reported with Grand Multipara (>4), 36 patients (72%) reported with Multipara (2-3), 2 patients (4%) reported with Nullipara and 10 patients (20%) reported with Primipara respectively.

Table 3: Distribution of study population based on the Chief Complaint

Serial No	Chief Complaint	No of Patients	Percentage (%)
1	Menometrorrhagia	19	38.0
2	Menorrhagia	11	22.0
3	Metrorrhagia	8	16.0
4	Polymenorrhagia	3	6.0
5	Post menopausal bleeding	9	18.0
	Total	50	100.0

Graph 3: Distribution of study population based on the Chief Complaint

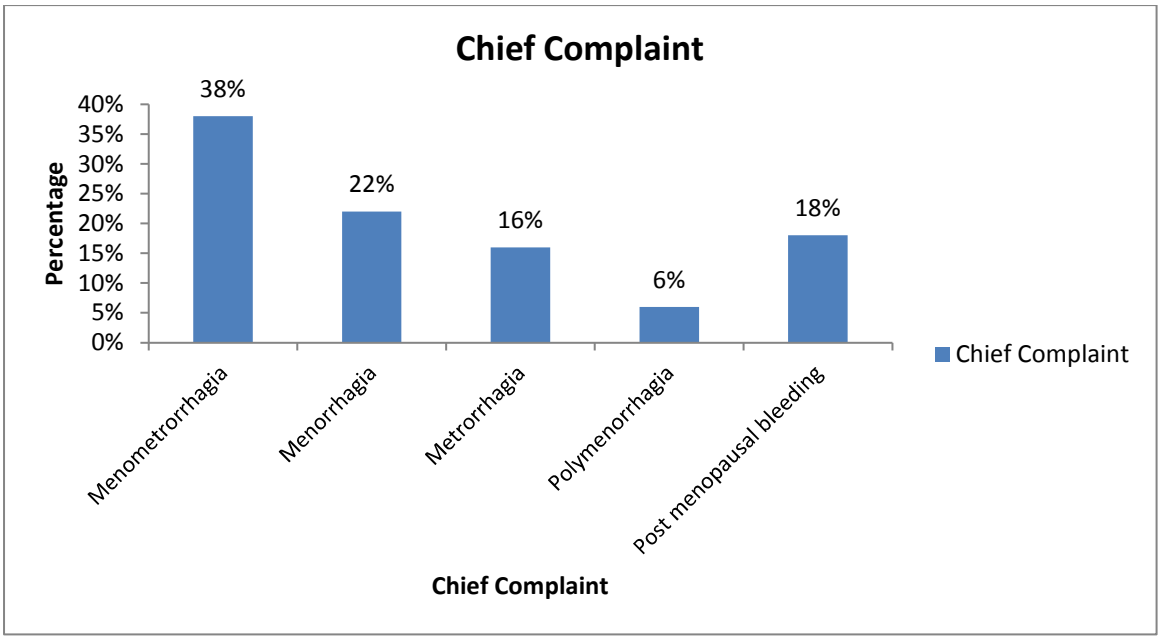


Table 3 and Graph 3 represent the Chief complaint as reported by the study population. It was observed that 19 patients (38%) reported with Menometrorrhagia, 11 patients (22%) reported with Menorrhagia (22%), 8 patients (16%) reported with Metrorrhagia, 3 patients (6%) reported with Polymenorrhagia and 9 patients (18%) reported with Post menopausal bleeding respectively.

Table 4: Distribution of study population based on the Histopathological Diagnosis

Serial No	Histopathological Diagnosis		No of Patients	Percentage (%)
1	Chronic Endometritis		1	2.0
2	Pill Endometrium		2	4.0
3	Simple Hyperplasia Without Atypia		26	52.0
4	Complex Hyperplasia Without Atypia		5	10.0
5	Complex Hyperplasia With Atypia		3	6.0
6	Endometrial Polyp		6	12.0
7	Endometrial Carcinoma (n=7 (14%))			
	7a	Endometrioid Adenocarcinoma	4	8.0
	7b	Endometrioid Adenocarcinoma with a focus of squamous metaplasia	2	4.0
	7c	Adenosquamous Carcinoma	1	2.0
	Total		50	100

Graph 4: Distribution of study population based on the Histopathological diagnosis

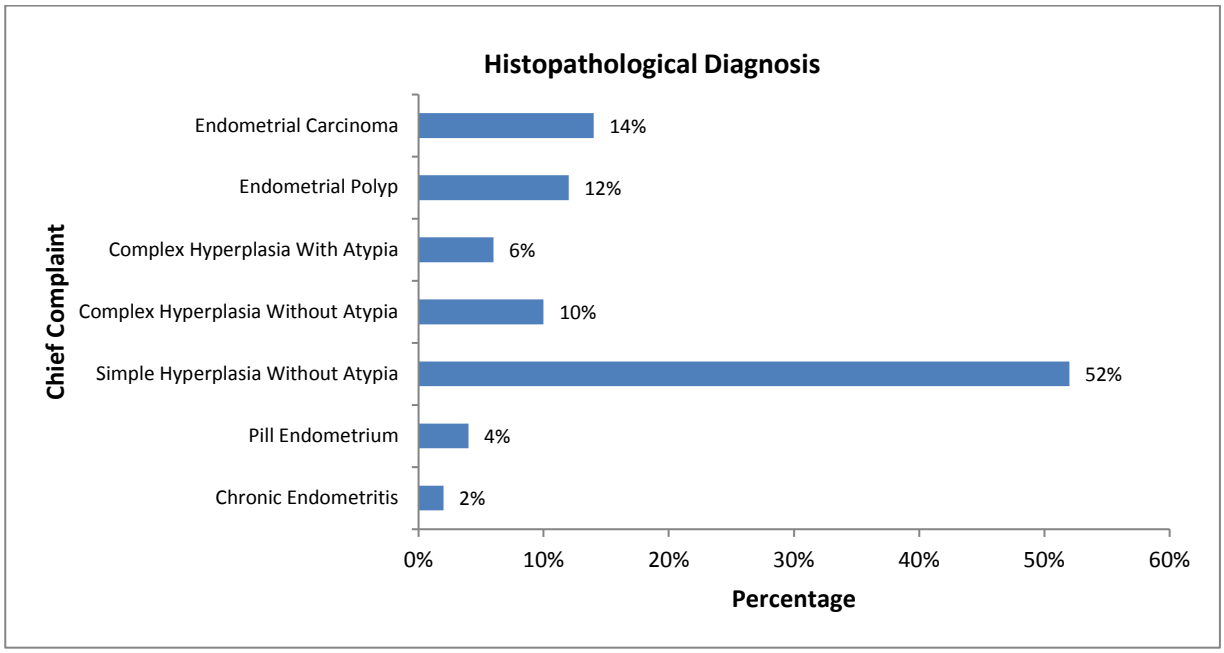


Table 4 and Graph 4 represent the Histopathological Diagnosis as reported by the study population. It was observed that there was 1 patient (2%) with Adenosquamous Carcinoma, 1 (2%) with Chronic Endometritis, 3 (6%) with Complex Hyperplasia With Atypia, 5 (10%) with Complex Hyperplasia Without Atypia, 6 (12%) with Endometrial Polyp, 4 (8%) with Endometrioid Adenocarcinoma, 2 (4%) with Endometrioid Adenocarcinoma With A Focus Of Squamous Metaplasia, 2 (4%) with Pill Endometrium, and 26 (52%) with Simple Hyperplasia Without Atypia.

Table 5: Distribution of study population as per the Histopathological findings in association to their Age groups

Histopathological Findings	No of patients & Percentage	Age Groups					Total
		Less than 40 years	41 to 50 years	51 to 60 years	61 to 70 years	More than 70 years	
Chronic Endometritis	n	1	0	0	0	0	1
	%	2.0%	0.0%	0.0%	0.0%	0.0%	2.0%
Pill Endometrium	n	1	1	0	0	0	2
	%	2.0%	2.0%	0.0%	0.0%	0.0%	4.0%
Simple Hyperplasia Without Atypia	n	9	16	1	0	0	26
	%	18.0%	32.0%	2.0%	0.0%	0.0%	52.0%
Complex Hyperplasia Without Atypia	n	4	1	0	0	0	5
	%	8.0%	2.0%	0.0%	0.0%	0.0%	10.0%
Complex Hyperplasia With Atypia	n	2	0	1	0	0	3
	%	4.0%	0.0%	2.0%	0.0%	0.0%	6.0%
Endometrial Polyp	n	3	2	1	0	0	6
	%	6.0%	4.0%	2.0%	0.0%	0.0%	12.0%
Endometrial Carcinoma	n	0	0	2	4	1	7
	%	0.0%	0.0%	4.0%	8.0%	2.0%	14.0%
Total	N	20	20	5	4	1	50
	%	40.0%	40.0%	10.0%	8.0%	2.0%	100.0%

Graph 5: Distribution of study population as per the Histopathological findings in association to their Age groups

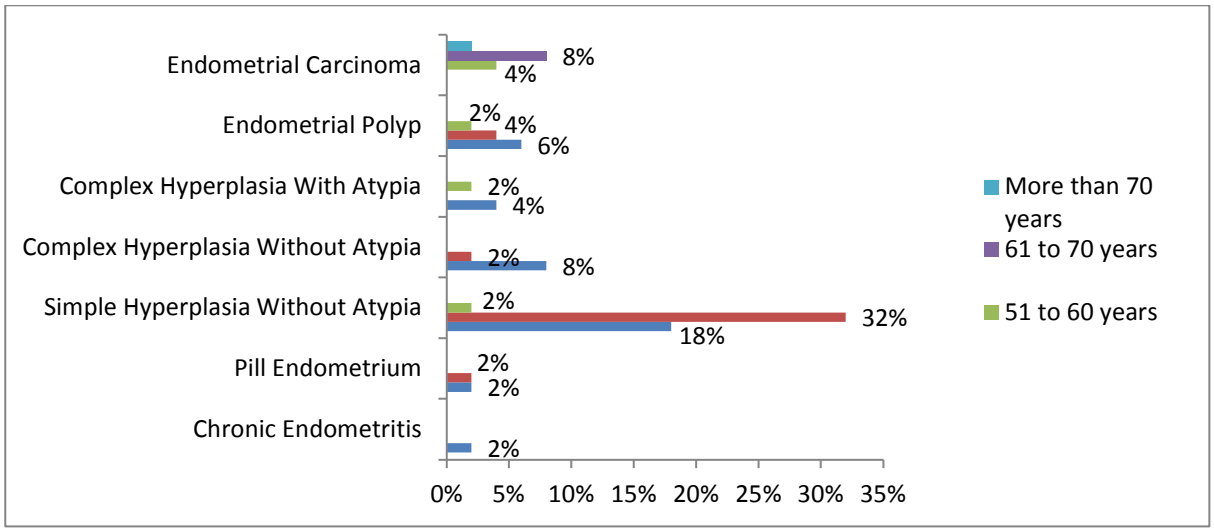


Table 6: Distribution of study population as per the Histopathological findings in association to Parity

Histopathological Findings	No of patients & Percentage	TYPES OF PARITY				Total
		GRAND MULTIPARA (>4)	MULTIPARA (2-3)	NULLIPARA	PRIMIPARA (1)	
Chronic Endometritis	n	0	0	0	1	1
	%	0.0%	0.0%	0.0%	2.0%	2.0%
Pill Endometrium	n	0	0	0	2	2
	%	0.0%	0.0%	0.0%	4.0%	4.0%
Simple Hyperplasia Without Atypia	n	1	20	2	3	26
	%	2.0%	40.0%	4.0%	6.0%	52.0 %
Complex Hyperplasia Without Atypia	n	0	3	0	2	5
	%	0.0%	6.0%	0.0%	4.0%	10.0 %

Complex Hyperplasia With Atypia	n	0	3	0	0	3
	%	0.0%	6.0%	0.0%	0.0%	6.0%
Endometrial Polyp	n	0	4	0	2	6
	%	0.0%	8.0%	0.0%	4.0%	12.0 %
Endometrial Carcinoma	n	1	6	0	0	7
	%	2.0%	12.0%	0.0%	0.0%	14.0 %
Total	N	2	36	2	10	50
	%	4.0%	72.0%	4.0%	20.0%	100.0 %

Graph 6: Distribution of study population as per the Histopathological findings in association to Parity

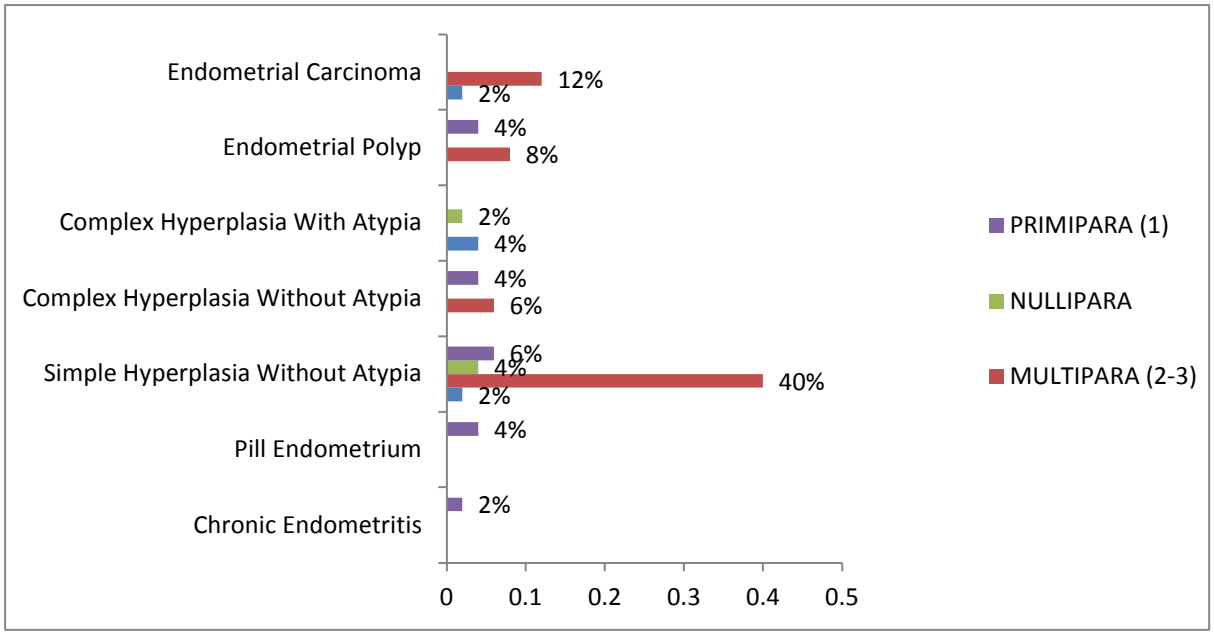
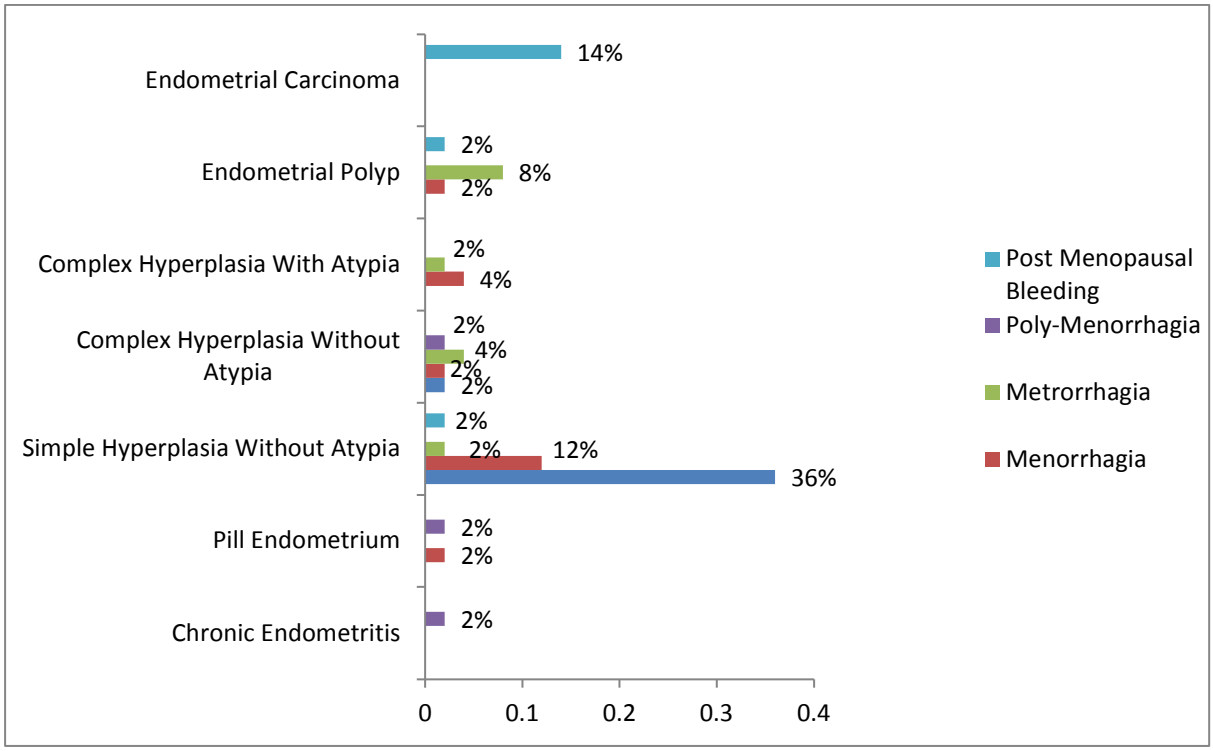


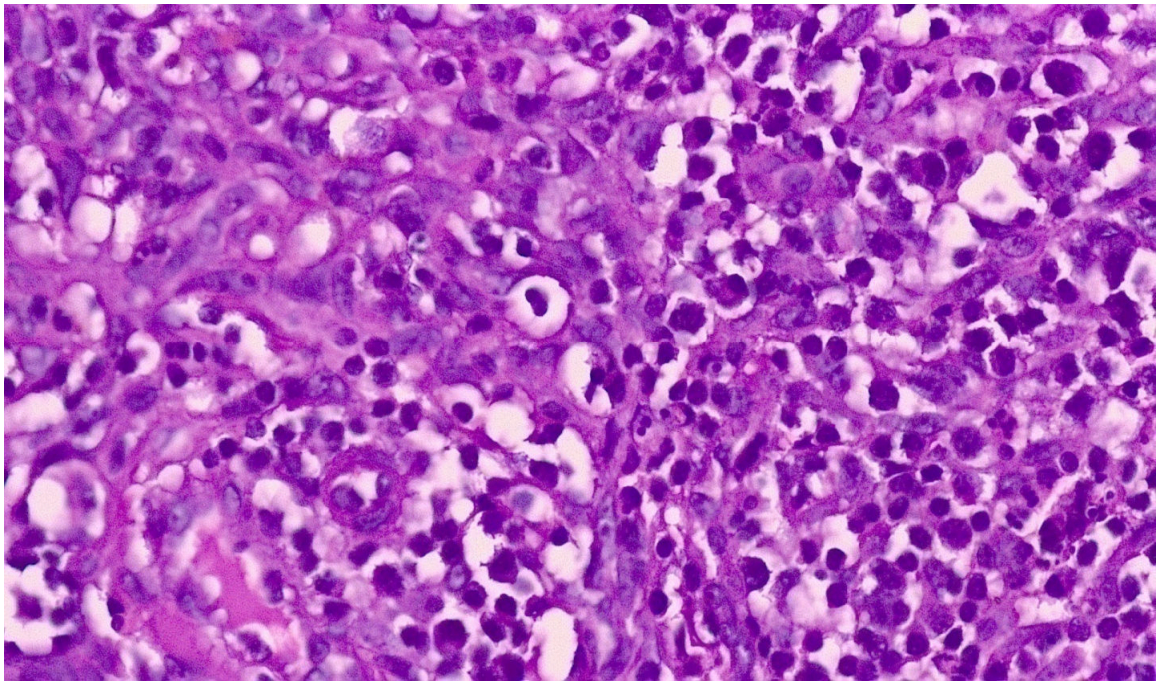
Table 7: Distribution of study population as per the Histopathological findings in association to Chief Complaints

Histopathological Findings	No Of Patients & Percentage	Chief Complaint					Total
		Menometro-rrhagia	Menorrhagia	Metrorrhagia	Poly-Menorrhagia	Post Menopausal Bleeding	
Chronic Endometritis	N	0	0	0	1	0	1
	%	0.0%	0.0%	0.0%	2.0%	0.0%	2.0%
Pill Endometrium	N	0	1	0	1	0	2
	%	0.0%	2.0%	0.0%	2.0%	0.0%	4.0%
Simple Hyperplasia Without Atypia	N	18	6	1	0	1	26
	%	36.0%	12.0%	2.0%	0.0%	2.0%	52.0 %
Complex Hyperplasia Without Atypia	N	1	1	2	1	0	5
	%	2.0%	2.0%	4.0%	2.0%	0.0%	10.0 %
Complex Hyperplasia With Atypia	N	0	2	1	0	0	3
	%	0.0%	4.0%	2.0%	0.0%	0.0%	6.0%
Endometrial Polyp	N	0	1	4	0	1	6
	%	0.0%	2.0%	8.0%	0.0%	2.0%	12.0 %
Endometrial Carcinoma	N	0	0	0	0	7	7
	%	0.0%	0.0%	0.0%	0.0%	14.0%	14.0 %
Total	N	19	11	8	3	9	50
	%	38.0%	22.0%	16.0%	6.0%	18.0%	100.0 %

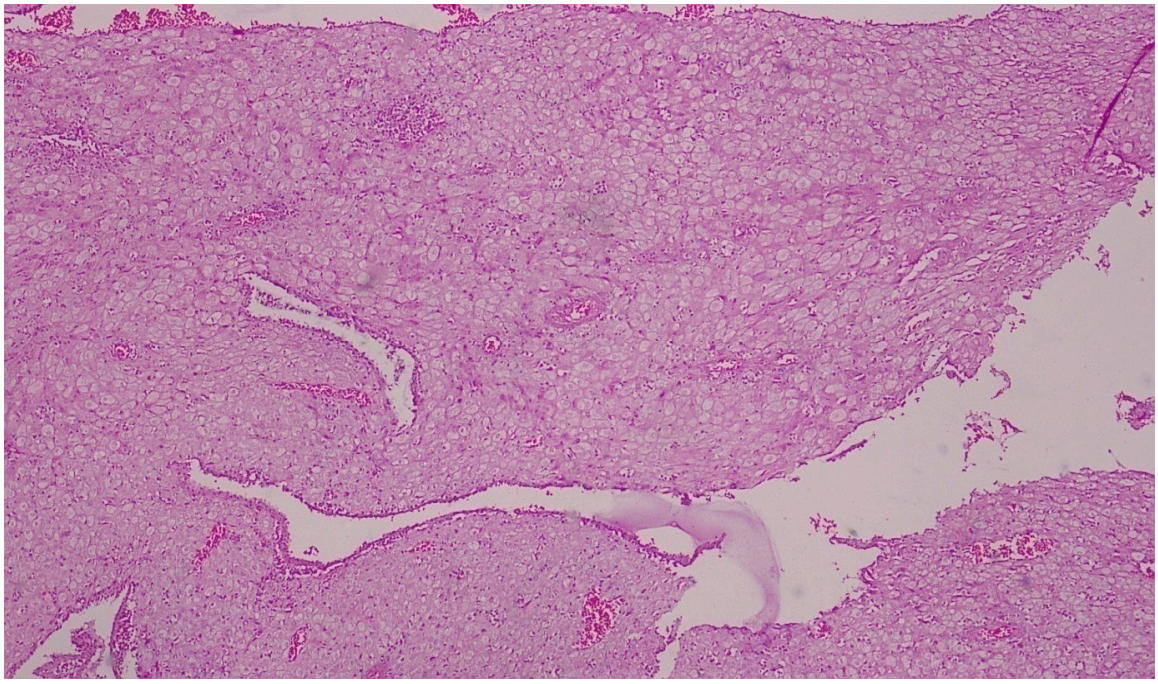
Graph 7: Distribution of study population as per the Histopathological findings in association to Chief Complaints



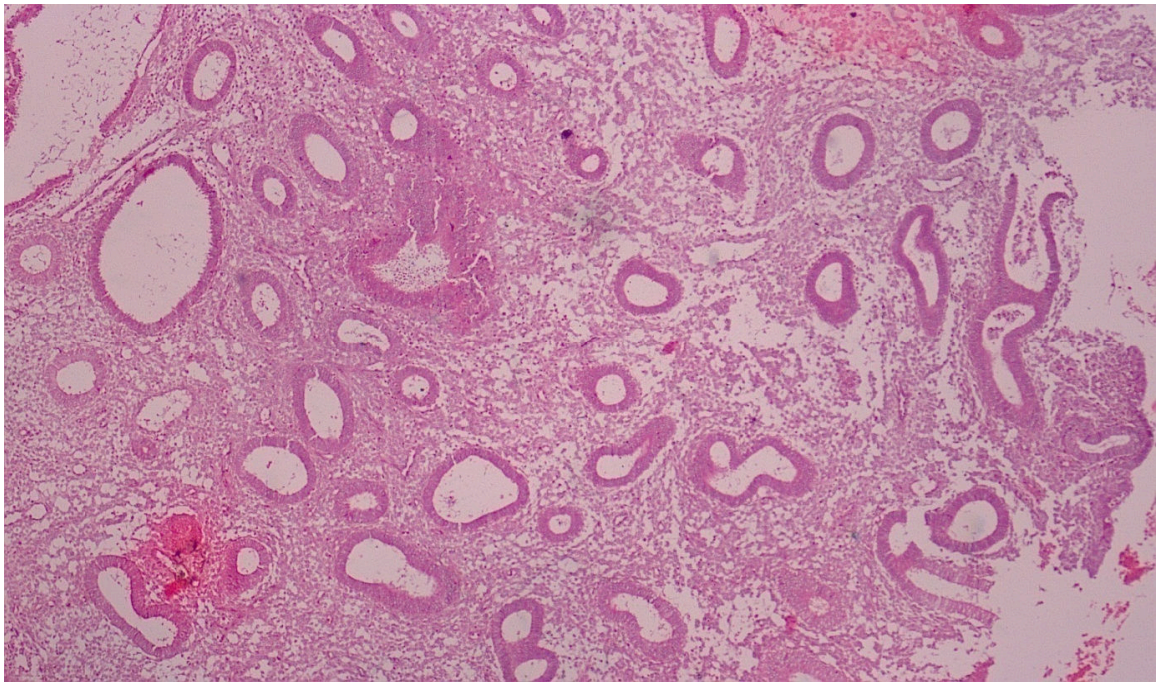
PHOTOMICROGRAPHS



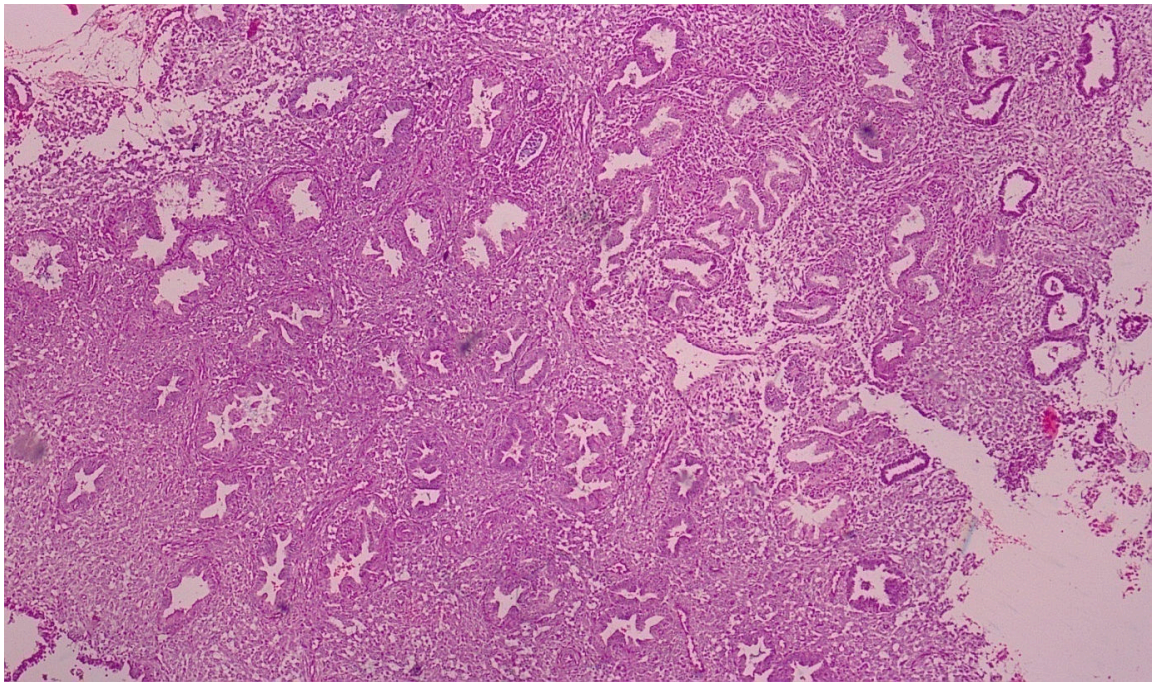
PHOTOMICROGRAPH 1: CHRONIC ENDOMETRITIS (H &E,40X)



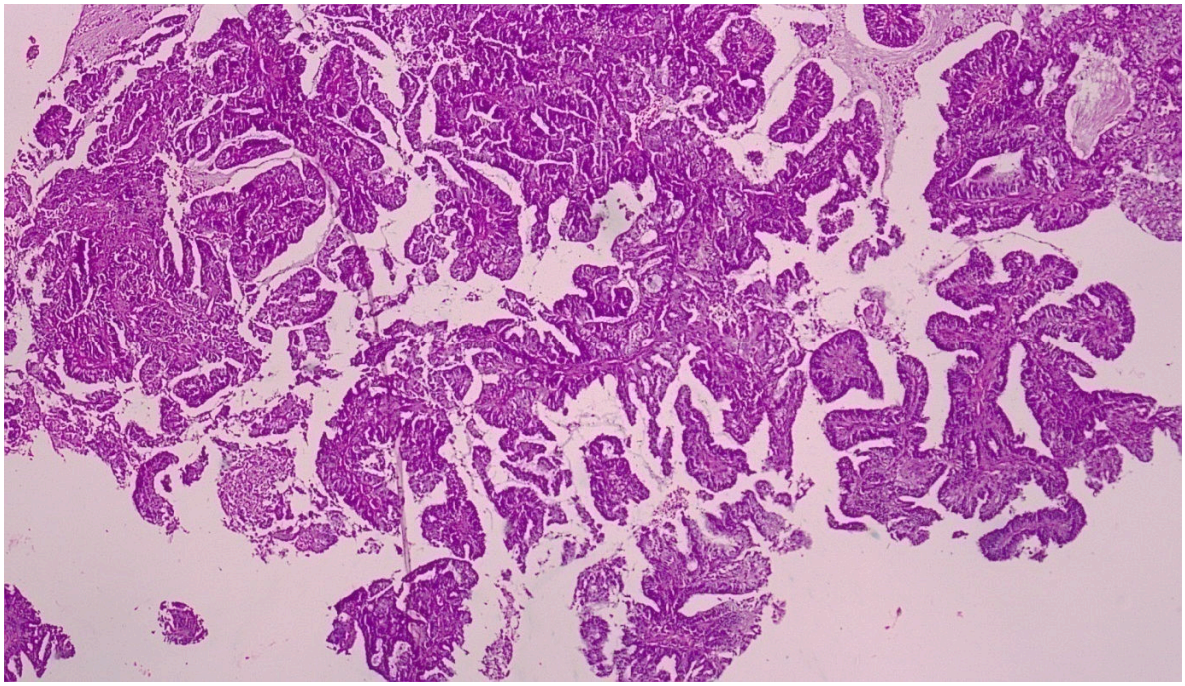
PHOTOMICROGRAPH 2: PILL ENDOMETRIUM (H&E,4X)



PHOTOMICROGRAPH 3: SIMPLE HYPERPLASIA WITHOUT ATYPIA (H&E,4X)

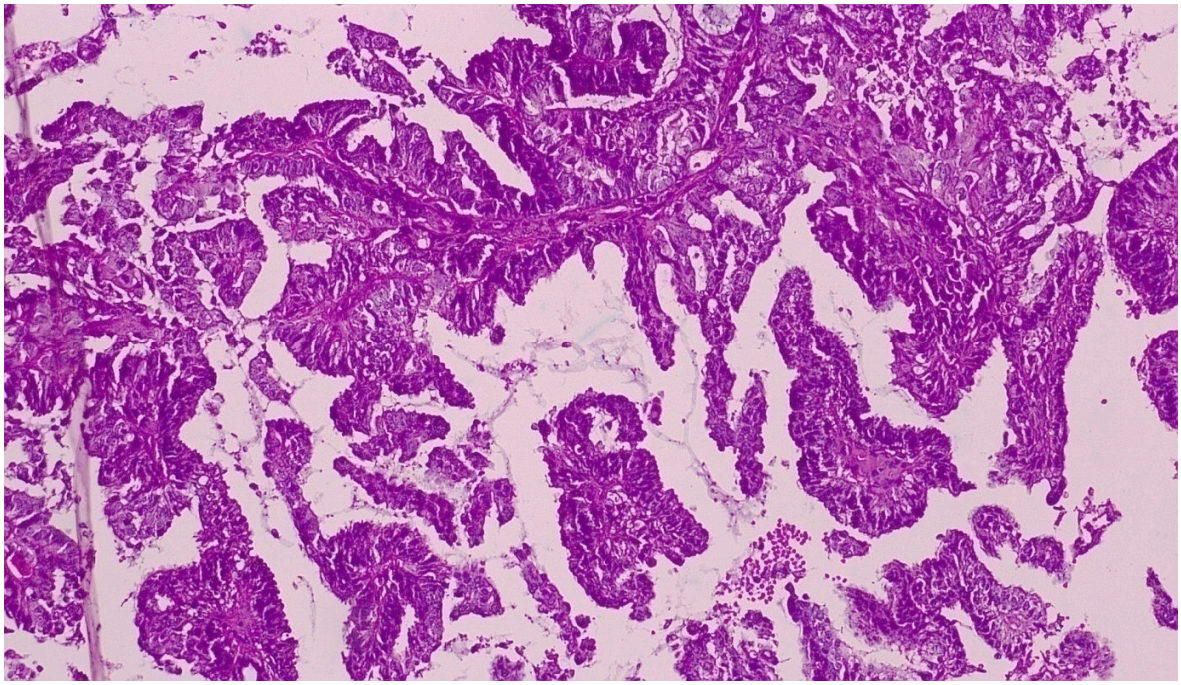


PHOTOMICROGRAPH 4: COMPLEX HYPERPLASIA WITHOUT ATYPIA(H&E,4X)



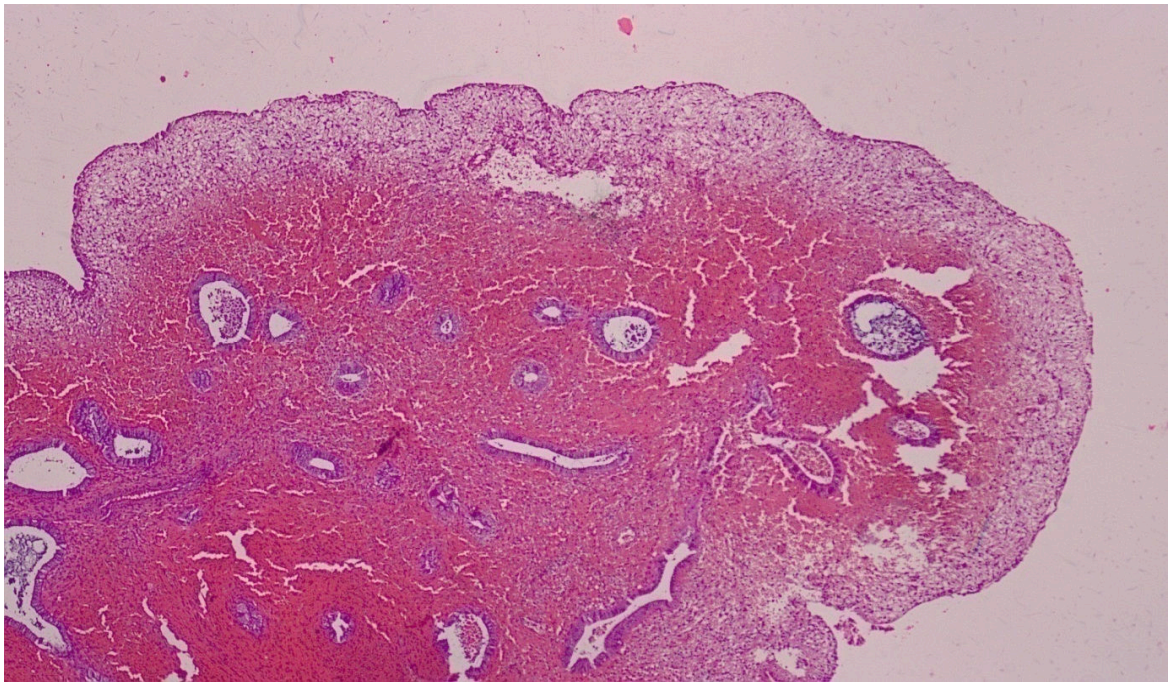
PHOTOMICROGRAPH 5a : COMPLEX HYPERPLASIA WITH ATYPIA

(H&E,4X)

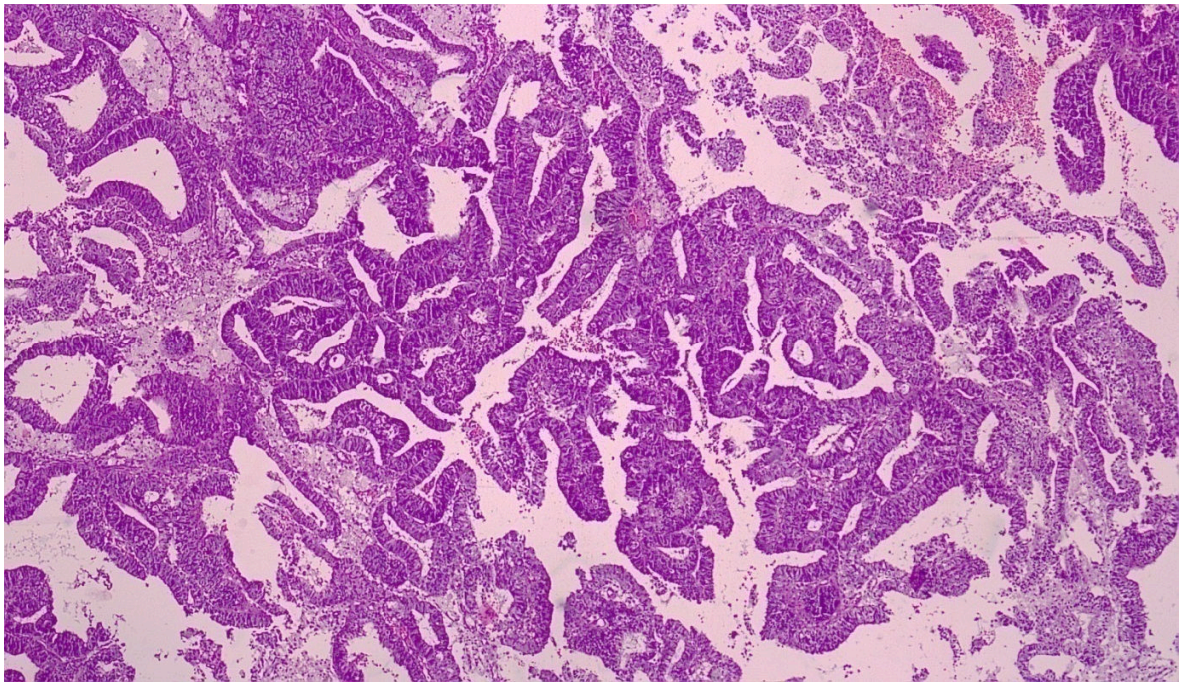


PHOTOMICROGRAPH 5b: COMPLEX HYPERPLASIA WITH ATYPIA

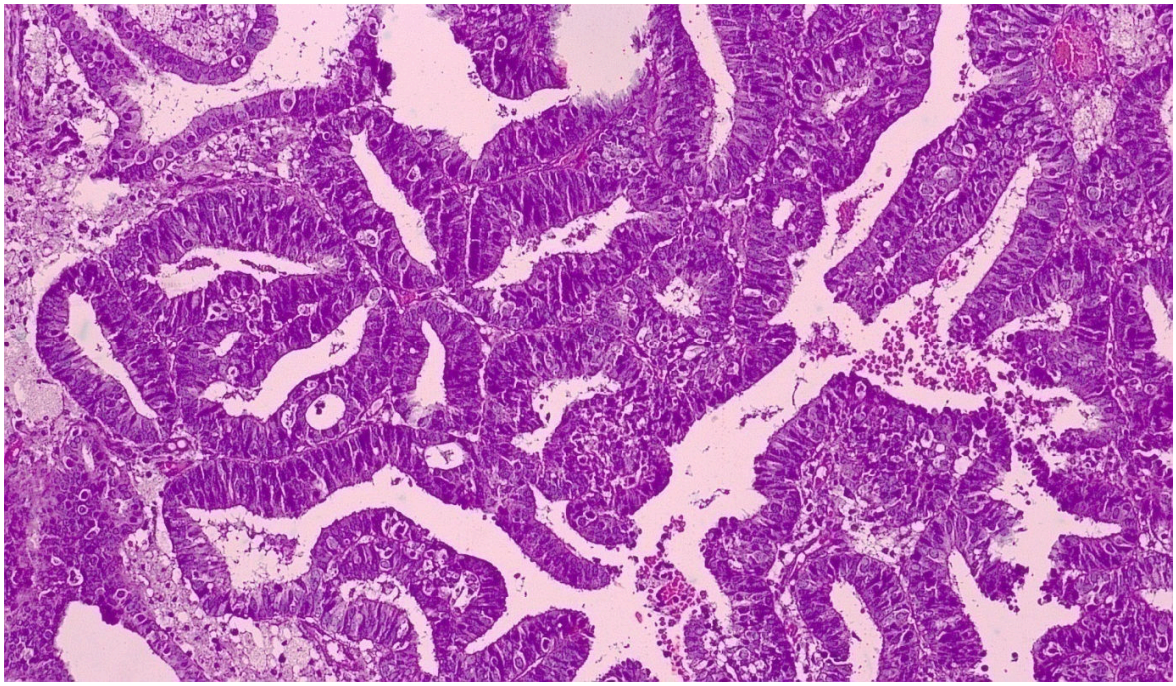
(H&E,10X)



PHOTOMICROGRAPH 6: ENDOMETRIAL POLYP (H&E,4X)

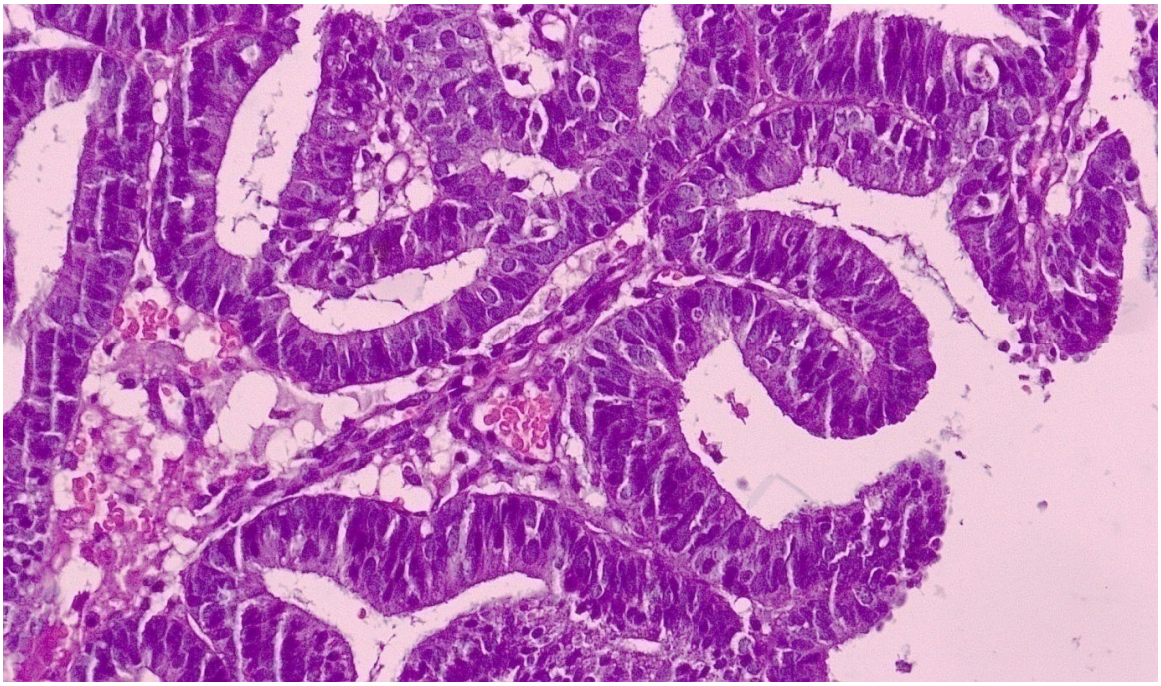


PHOTOMICROGRAPH 7a: ENDOMETRIOID ADENOCARCINOMA (H&E,4X)



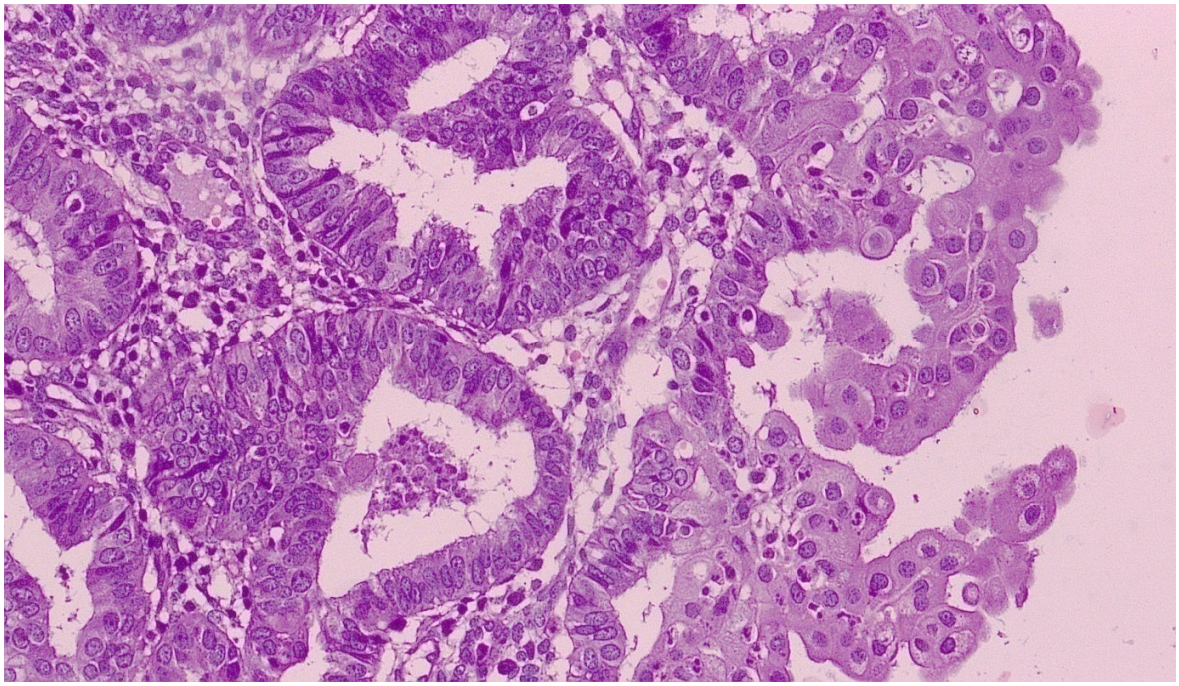
PHOTOMICROGRAPH 7b: ENDOMETRIOID ADENOCARCINOMA

(H&E,10X)

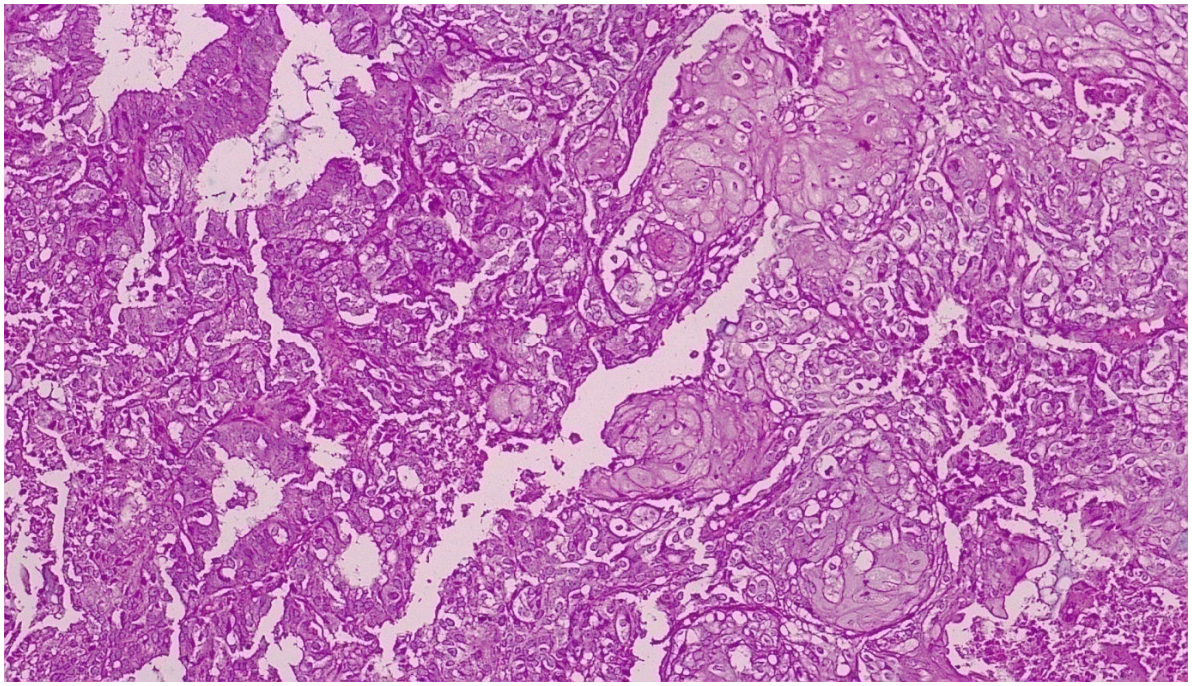


PHOTOMICROGRAPH 7c: ENDOMETRIOID ADENOCARCINOMA

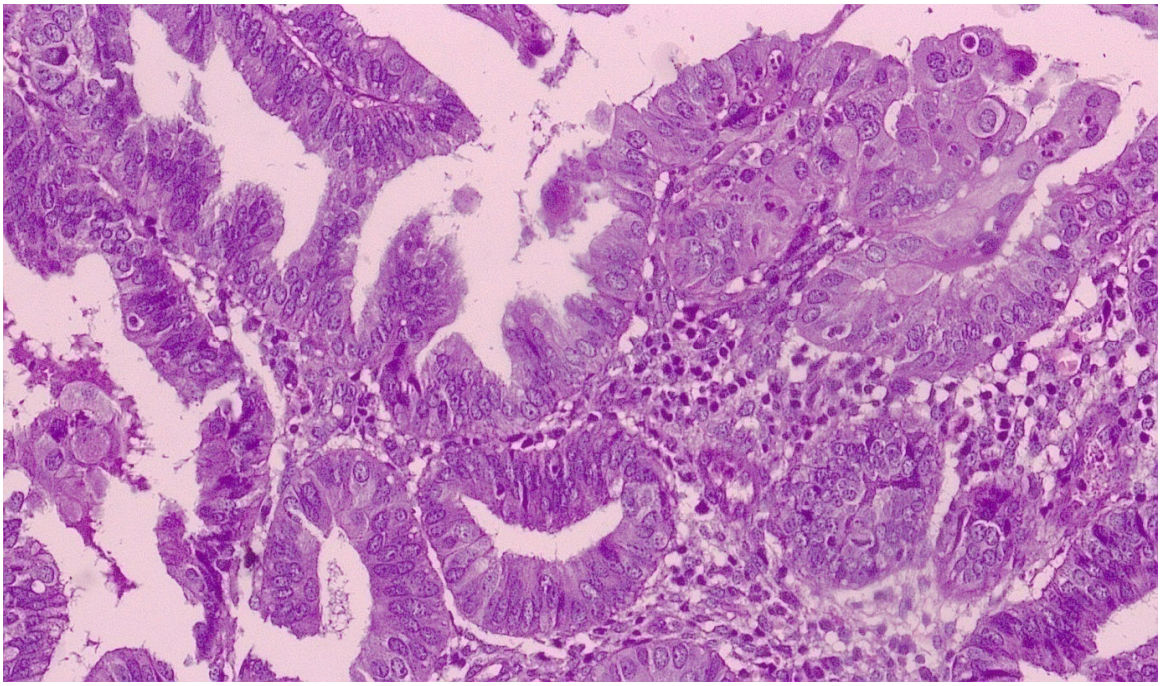
(H&E,20X)



PHOTOMICROGRAPH 8: ENDOMETRIOID ADENOCARCINOMA WITH A FOCUS OF SQUAMOUS METAPLASIA (H&E,20X)



PHOTOMICROGRAPH 9a: ADENOSQUAMOUS CARCINOMA (H&E,10X)



PHOTOMICROGRAPH 9b: ADENOSQUAMOUS CARCINOMA (H&E,20X)

DISCUSSION

Endometrium is prone for pathological lesion which is hormonally sensitive, responsive and undergoes changes throughout life of a female.AUB is one of the commonest complaints in patients who then consults a gynaecologist.[22]

Endometrial curettage is the most common procedure practised to assess the cause of the bleeding.In this procedure scrapping of endometrial lining is taken and histopathological examination of the tissue is done.[22]

The highest incidence of Abnormal uterine bleeding was noted in the age group of 35-40(40%) and 41-50(40%) years in the present study which is in concordance with the result of studies done by Kulwinder et al[74](54%), Kalpana et al[75](52%), Sharma J et al[43](31%).

In the present study, patients presented with different types of AUB; the commonest being menometrorrhagia (38%) followed by menorrhagia (22%). A study done by Bodhisatwa et al.[74] found that the most common symptom in their study was menorrhagia (57.12%) followed by metrorrhagia (12.23%) and then menometrorrhagia (2.74%).

In the present study, the highest incidence of abnormal uterine bleeding was seen in multiparous women(72%),which is in concordance with the results of the studies done by Mehrotra VG et al[54](46%), Bhattacharji et al[55](46%), Sadia et al[76](54%) .The lowest incidence was seen in nulliparous women in the present study(4%) which is in concordance with the results of the studies by Anusuya D et al[61](18%), Bhattacharjee et al[55](18.8%), Sadia K et al[49](5.4%) .By these observations, it may be implied that the incidence of AUB is highest in parous women in general(96%in this study) and multiparous in particular(72%).

COMPARATIVE STUDY OF INCIDENCE OF ENDOMETRIAL HYPERPLASIA IN AUB

AUTHOR	YEAR	NUMBER	PERCENTAGE WITH ENDOMETRIAL HYPERPLASIA
Sutherland[22]	1950	1000	15.5%
Joshi and Deshpande[62]	1964	208	19%
Bhattacharji et al [55]	1964	164	29.2%
Anusuya D et al[61]	1964	117	30.6%
Mehrotra VG et al [54]	1972	150	19.4%
Pilli et al [64]	2002	100	44%
Talat Mirza et al [72]	2012	1000	13%
Bhagat et al[58]	2019	465	9.03%
Present Study	2021	50	52%

In this study simple hyperplasia without atypia was the most common pattern seen in 26 cases(52%).This study was in coordination with Talaudar et al[(77)](41.66%), Sanjitha et al[(50)](25%) ,Dangal G[(75)](30.7%), Gredmark et al[(76)](30%), however the incidence was a bit on the lower side in the studies done by Sudhamani et al[(78)](20.74%) and Jairapuri et al[(65)](5.79%).Endometrial hyperplasia is a very common histopathological diagnosis in perimenopausal age group. Followed by this the second most common pattern was

endometrial polyp seen in 6 cases (12%).Other studies reported a lower incidence. Next up was complex hyperplasia without atypia and was seen in 5 cases (10%) and complex hyperplasia with atypia seen in 3 cases(6%).

COMPARATIVE STUDY OF INCIDENCE OF ENDOMETRIAL ADENOCARCINOMA IN AUB

AUTHORS	YEAR	NUMBER	PERCENTAGE
Khare A et al[40]	2012	3/187	1.6%
Bhatta S et al[42]	2012	7/122	5.74%
Sharma J et al[43]	2013	1/195	0.51%
Shah R et al[41]	2014	1/80	0.3%
Bagat et al[58]	2019	6/465	9.03%
Present Study	2021	06/50	12%

In the present study, the incidence of endometrial carcinoma was seen in women within age group of 51-70 years, presenting with chief complaints of post menopausal bleeding. Total number of endometrial carcinoma cases were 7(14%).The result of this study was almost similar to the data mentioned by Yusuf et al[(79)] and Escoffery et al[(80)] in their study. This is also similar to what was reported by Baral et al.[(81)] Out of these the predominant type of endometrial carcinoma was endometrioid type which constituted 4 cases(8%).All the four were classical endometrioid type while the two of them were

showing squamous differentiation. Out of these seven cases one of the case was showing adenosquamous carcinoma. This study has more carcinoma cases as this is a tertiary care center/referral center with a well equipped oncopathology laboratory and secondly because the sample size is less. Increased BMI and chronic anovulation has been implicated as a cause of endometrial adenocarcinoma.

Amongst the other organic causes causing Abnormal uterine bleeding were pill endometrium and chronic endometritis.

CONCLUSION

AUB is one of the common gynaecological problems encountered in clinical practice and is defined as abnormal bleeding from the uterus in the abscence of an organic lesion to account for.

Endometrium is a mirror of histopathology for the hormone dependant and non hormone dependant causes of AUB in different age groups and is important in detecting the cause clinching the diagnosis and treatment of the patient.

Endometrial biopsy can be easily procured in AUB cases by D&C, which is a simple, cost effective and appropriate method that provides accurate diagnostic yield .The present study highlights the importance of endometrial biopsy and its interpretation which play a pivotal role in management of AUB.

In the present study , menometrorrhagia was the commonest presenting symptom and multiparous women were the most affected by AUB. The commonest histopathological finding encountered was simple hyperplasia without atypia which was seen mostly in patients in the age group of 41-50. Next most common cause was endometrial polyp. Out of the 50 cases 7 were of endometrial carcinoma. In this one case had adenosquamous carcinoma, 4 cases were of endometrioid carcinoma and 2 cases were of endometrioid carcinoma with a focus of squamous carcinoma.

SUMMARY

Study of endometrial histopathology in perimenopausal and post menopausal women with abnormal uterine bleeding is helpful to diagnose hyperplasia and carcinoma of endometrium.

Endometrial biopsy has for many years been the method of choice for the diagnosis of endometrial cancer in patients with peri and postmenopausal bleeding. Apart from it, it reveals from inflammatory condition to simple hyperplasia, complex hyperplasia to carcinomas.

In this study the age group ranged from 35 years to more than 70 years. Out of this 2 patients were grand multipara(>4), 6 patients were multipara(2-3), 2 patients were nullipara and 10 patients were primipara(1).

The presenting complaints of 19 patients were menometrorrhagia,11 had menorrhagia, 8 patients presented with metrorrhagia, 3 patients polymenorrhagia and 9 complained of post menopausal bleeding.

On histopathological diagnosis,1 patient had chronic endometritis, 2 patients had pill endometrium, 26 cases had simple hyperplasia without atypia,5 cases had complex hyperplasia without atypia , 3 cases had complex hyperplasia with atypia and 7 cases were of endometrial carcinomas. Out of these 7 cases ,4 cases had endometrioid adenocarcinoma (typeI), 2 had endometrioid adenocarcinoma with a focus of squamous metaplasia and 1 had adenosquamous carcinoma.

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ANNEXURE I

INFORMED CONSENT

HISTOPATHOLOGICAL STUDY OF ENDOMETRIUM IN PATIENTS PRESENT WITH ABNORMAL UTERINE BLEEDING

Purpose of the study: You are being asked to enroll in this study as you are eligible for participation in this study. If you undergo dilatation and curettage you will be included in this study.

The purpose of this study is to evaluate various histopathological features obtained by dilatation and curettage along with sonographic finding wherever possible in patients presenting with abnormal uterine bleeding.

Procedure: During this study, you will be asked questions regarding history and background and you are supposed to answer to the best of your knowledge .

If you agree to enroll yourself in this study, you will be interviewed regarding your present, past and family history and your clinical manifestations.

Risks and benefits: There are no risks involved in taking part in this study and benefit is we will be able to find out the cause/ diagnose the cause of abnormal uterine bleeding.

Alternatives: Taking part in this study is voluntary. You may choose not to take part in this study or if you decide to take part now, you can later change your mind and withdraw from the study. The study doctor or sponsor may terminate your participation in this study anytime.

Privacy and confidentiality: All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study will be published but

your identity will be confidential in any publication. No information about you or information provided by you during research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Financial incentives for participation: You will not be paid / offered any gift /incentives for participating in this study.

Authorization to publish results: The results of this study would be forwarded to the KLE University, Belagavi as a part of requirement towards the completion of MD degree, review and publishing.

CONSENT STATEMENT

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form and have had all my questions answered.

In case of the queries during the study or in future you may contact following person.

Principal Investigator:

Guide :

Name of the participant:

(signature/thumbprint)

Name of the witness : (signature)

Name of the investigator: (signature)

Date:

Address:

Phone no

ANNEURE II- ETHICAL CLEARANCE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed to be University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)

JAWAHARLAL NEHRU MEDICAL COLLEGE,
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Ref: MDC/DOME/ 376 **Date: 16/06/2020**

To,

BN0119008
PG student in Pathology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"HISTOPATHOLOGICAL STUDY OF ENDOMETRIUM IN PATIENTS PRESENTING WITH ABNORMAL UTERINE BLEEDING"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE III

PROFORMA

PATIENT HISTORY

Name : Age :

IP no. :

Brief clinical history :

1.History of receiving any hormonal therapy -

2.History of any gynaecological procedure done –

3.Parity-

EXAMINATION FINDINGS

Ultrasound findings(if any):

Size of the endometrium:

CLINICAL DIAGNOSIS :

HISTOPATHOLOGICAL DIAGNOSIS : Hematoxylin and Eosin staining :

- DILATATION AND CURETTAGE:

ANNEURE IV

HEMATOXYLIN AND EOSIN STAINING

- Deparaffinize in Xylene I and II and III changes. [III change use warmed xylene](5 minutes in each)
- Rehydrate using:
    - Absolute Ethanol 100% (5 minutes)
    - Absolute Ethanol 100% (5 minutes)
- Rinse in distilled water (5 minutes)
- Rinse in running tap water (5 minutes)
- Stain in Harris's hematoxylin by progressive method (2 minutes) **Fresh andfiltered**
- Rinse in running tap water (20 minutes)
- Decolorize in 1% acid alcohol (1 second)
- Rinse well in tap water (5 minutes)
- Immerse in hot water bath, 550 C for bluing (3 Seconds)
- Rinse in tap water (5 minutes)
- Counterstain in Eosin (15 seconds)
- Dehydrate absolute alcohol 100 % (2-4 dips)
- Clear in Xylene I and II (5 minutes)
- Mount with DPX.

Stock Solutions- EOSIN:

Stock- 1% aqueous Eosin-Y

Stock- 1% aqueous Phloin B

Working Solution- EOSIN:

100ml stock Eosin

10ml stock Phliin B

780ml 95% Ethanol

4ml glacial Acetic Acid

Working Solution: **Hematoxylin**

Harris Hematoxylin, 1 Liter

Working Solution:- **0.25% Acid Alcohol**

95% Ethanol ,2578 ml

dH2O, 950ml

HCL, 9ml

Results: Nuclei-Blue, cytoplasm-Pink, RBCs-Red.

Reference: Bancroft D, Laylon C. The hematoxylin and eosin, In: Kim SS Ed Bancroft's Theory and practise of histopathological techniques. 7th Ed., China, Churchill Livingstone;2013:173-187.

ANNEXURE V
(MASTER CHART)

SL NO	IP NO	HP NO	NAME	AGE	TYPES OF PARITY	CHIEF COMPLAINT	USG FINDINGS	CLINICAL DIAGNOSIS	HISTOPATHOLOGICAL DIAGNOSIS
1	997668	0597/20	SUMITRA	42	MULTIPARA(2-3)	MENORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
2	997678	0321/20	SHRUTHI	45	MULTIPARA (2-3)	MENORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
3	1040226	604/19	MEENAKSHI	43	PRIMIPARA(1)	POLYMENORRHAGIA		ABNORMAL UTERINE BLEEDING	PILL ENDOMETRIUM
4	995807	0229/20	SITA	40	MULTIPARA (2-3)	MENORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
5	994996	0153/20	JYOTHI	46	MULTIPARA (2-3)	MENORRHAGIA	13.6MM	ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
6	93311	007/20	SUPRIYA	40	PRIMIPARA (1)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	COMPLEX HYPERPLASIA WITHOUT ATYPIA
7	1037448	15/20	SARASWATI YALL	40	MULTIPARA (2-3)	MENORRHAGIA		ABNORMAL UTERINE BLEEDING	COMPLEX HYPERPLASIA WITH ATYPIA
8	329355	0052/20	SUMAN	60	MULTIPARA (2-3)	POST MENOPAUSAL BLEEDING		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
9	1000777	548/20	JADADEVI	57	PRIMIPARA (1)	POST MENOPAUSAL BLEEDING	12.7MM	ABNORMAL UTERINE BLEEDING	ENDOMETRIAL POLYP
10	1001110	582/20	AKSHATHA	41	MULTIPARA (2-3)	MENORRHAGIA		ABNORMAL UTERINE BLEEDING	ENDOMETRIAL POLYP
11	958707	2749/20	YAMANNAVA	37	NULLIPARA	MENORRHAGIA	11MM	ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
12	20015123	1255/20	SHOBHA	74	MULTIPARA (2-3)	POST MENOPAUSAL BLEEDING	23MM	POST MENOPAUSAL BLEEDING	ADENOSQUAMOUS CARCINOMA
13	10007211	994/20	MAHADEVI	44	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
14	20004782	37/20	LEELAVATI	54	MULTIPARA (2-3)	POST MENOPAUSAL BLEEDING	20MM	ABNORMAL UTERINE BLEEDING	ENDOMETRIOID ADENOCARCINOMA WITH A FOCUS OF SQUAMOUS METAPLASIA
15	21001664	16/19	SHOBHA	49	MULTIPARA (2-3)	METRORRHAGIA		ABNORMAL UTERINE BLEEDING	ENDOMETRIAL POLYP
16	20288045	111/20	URMILA MAHADEV	45	MULTIPARA (2-3)	POLYMENORRHAGIA		ABNORMAL UTERINE BLEEDING	COMPLE HYPERPLASIA WITHOUT ATYPIA
17	20109666	904/20	ANURADHA	37	PRIMIPARA (1)	POLYMENORRHAGIA		ABNORMAL UTERINE BLEEDING	CHRONIC ENDOMETRITIS
18	20118845	966/20	POORNIMA	40	PRIMIPARA(1)	METRORRHAGIA		ABNORMAL UTERINE BLEEDING	ENDOMETRIAL POLYP
19	1039150	517/19	NIRMALA	39	PRIMIPARA (1)	MENORRHAGIA		ABNORMAL UTERINE BLEEDING	PILL ENDOMETRIUM
20	1036445	279/19	MALLAVA	39	MULTIPARA (2-3)	METRORRHAGIA		ABNORMAL UTERINE BLEEDING	COMPLEX HYPERPLASIA WITHOUT ATYPIA
21	992577	0015/20	SARASWATI	48	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
22	3033304	1422/20	SUSHMA	45	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
23	3033575	1475/20	ANNASUYA	40	MULTIPARA (2-3)	MENOMETRORRHAGIA	14.5MM	ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA

24	1007675	961/20	GEETA	40	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
25	3031248	935/20	PRAGATI	45	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
26	1014651	1261/20	BHARATI	49	GRAND MULTIPARA(>4)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
27	1012498	1113/20	URMILA	45	MULTIPARA(2-3)	MENORRHAGIA	14MM	ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
28	1012509	1110/20	VENKATAMMA	48	MULTIPARA(2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
29	3036517	1862/20	GIRIJA	49	PRIMIPARA (1)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
30	993311	73/20	SUPRIYA	40	MULTIPARA (2-3)	MENORRHAGIA		ABNORMAL UTERINE BLEEDING	COMPLEX HYPERPLASIA WITH ATYPIA
31	20121308	996/20	KAHEKASHA	40	MULTIPARA (2-3)	METRORRHAGIA		ABNORMAL UTERINE BLEEDING	ENDOMETRIAL POLYP
32	20199387	1698/20	PADMAVATI	43	PRIMIPARA (1)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
33	1033405	52/20	SUMAN	60	MULTIPARA (2-3)	METRORRHAGIA		ABNORMAL UTERINE BLEEDING	COMPLE HYPERPLASIA WITH ATYPIA
34	18253509	2741/19	DWARKA	67	GRAND MULTIPARA(>4)	POST MENOPAUSAL BLEEDING	22MM	POST MENOPAUSAL BLEEDING	ENDOMETRIOID ADENOCARCINOMA
35	18263062	2861/19	CINCILLA	63	MULTIPARA (2-3)	POST MENOPAUSAL BLEEDING	20MM	POST MENOPAUSAL BLEEDING	ENDOMETRIOID ADENOCARCINOMA WITH A FOCUS OF SQUAMOUS METAPLASIA.
36	18264421	2879/20	LAXMI BAI	65	MULTIPARA (2-3)	POST MENOPAUSAL BLEEDING	20.05MM	POST MENOPAUSAL BLEEDING	ENDOMETRIOID AENOCARCINOMA
37	932954	1523/20	PARVATI	37	PRIMIPARA (1)	METRORRHAGIA		ABNORMAL UTERINE BLEEDING	COMPLEX HYPERPLASIA WITHOUT ATYPIA
38	990407	5930/20	SUMITRA	40	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
39	981754	5481/20	NAGAVVA	40	MULTIPARA(2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
40	3024974	4126/20	SUSHILA	43	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
41	958863	4160/20	MALLAVA	39	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
42	966574	4456/20	LAXMI	45	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
43	18299246	3240/20	RENUKA	60	MULTIPARA (2-3)	POST MENOPAUSAL BLEEDING		POST MENOPAUSAL BLEEDING	ENDOMETRIOID ADENOCARCINOMA
44	18400363	4040/20	SAKUNTALA	70	MULTIPARA (2-3)	POST MENOPAUSAL BLEEDING		POST MENOPAUSAL BLEEDING	ENDOMETRIOID ADENOCARCINOMA
45	20199386	1697/20	SUSHMA	39	MULTIPARA (2-3)	MENORRHAGIA		ABNORMAL UTERINE BLEEDING	COMPLEX HYPERPLASIA WITHOUT ATYPIA
46	20196690	1667/20	GIRIJA H	42	MULTIPARA (2-3)	MENOMETRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
47	21003981	49/19	SUJATA	38	MULTIPARA (2-3)	METRORRHAGIA		ABNORMAL UTERINE BLEEDING	ENDOMETRIAL POLYP
48	946184	2960/20	NAZEYA	37	NULLIPARA	METRORRHAGIA		ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
49	3021523	2007/20	JAYASHREE	37	PRIMIPARA (1)	MENOMETRORRHAGIA	12MM	ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA
50	920832	0152/20	GANGAVVA	50	MULTIPARA (2-3)	MENOMETRORRHAGIA	14.5MM	ABNORMAL UTERINE BLEEDING	SIMPLE HYPERPLASIA WITHOUT ATYPIA