HISTOPATHOLOGICAL ANALYSIS OF ENDOMETRIAL CHANGES IN ASSOCIATION WITH MYOMETRIAL LESIONS OF HYSTERECTOMY SPECIMENS

DISSERTATION SUBMITTED TO

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY,

CHENNAI – 600032.

In partial fulfilment of the requirement for the degree of Doctor of Medicine in Pathology (Branch III)

M.D.(PATHOLOGY)

APRIL 2019

DEPARTMENT OF PATHOLOGY

TRICHY SRM MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE

TRICHY – 621105

DECLARATION

I solemnly declare that the dissertation entitled **"HISTOPATHOLOGICAL ANALYSIS OF ENDOMETRIAL CHANGES IN ASSOCIATION WITH MYOMETRIAL LESIONS OF HYSTERECTOMY SPECIMENS".**

Is a bonafide research work done by me in the Department of Pathology at Trichy SRM Medical College Hospital and Research Centre, Trichy during the two year period from 2016 to 2018 under the guidance and supervision of **Dr.K.AMBEDKAR RAJ M.D.,** Professor, Department of Pathology, TSRMMCH & RC , Trichy.

This dissertation is submitted to THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY, Chennai towards the partial fulfilment of the requirement for the award of M.D.,Degree (Branch III)in Pathology.

I have not submitted this dissertation on any previous occasion to any university for the award of any degree.

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CERTIFICATE

This is to certify that the dissertation entitled **"HISTOPATHOLOGICAL ANALYSIS OF ENDOMETRIAL CHANGES IN ASSOCIATION WITH MYOMETRIAL LESIONS OF HYSTERECTOMY SPECIMENS"** is a record of bonafide work done by Dr.R.Rathika, postgraduate student in the Department of Pathology, during the course of study (2016 – 2018), Trichy SRM Medical College Hospital and Research Centre, Trichy under the supervision and guidance of **Dr.K.Ambedkar raj, M.D.**

This dissertation is a record of authentic work done by the candidate, **Dr.R. Rathika.** This work was carried out by the candidate herself under my supervision**.**

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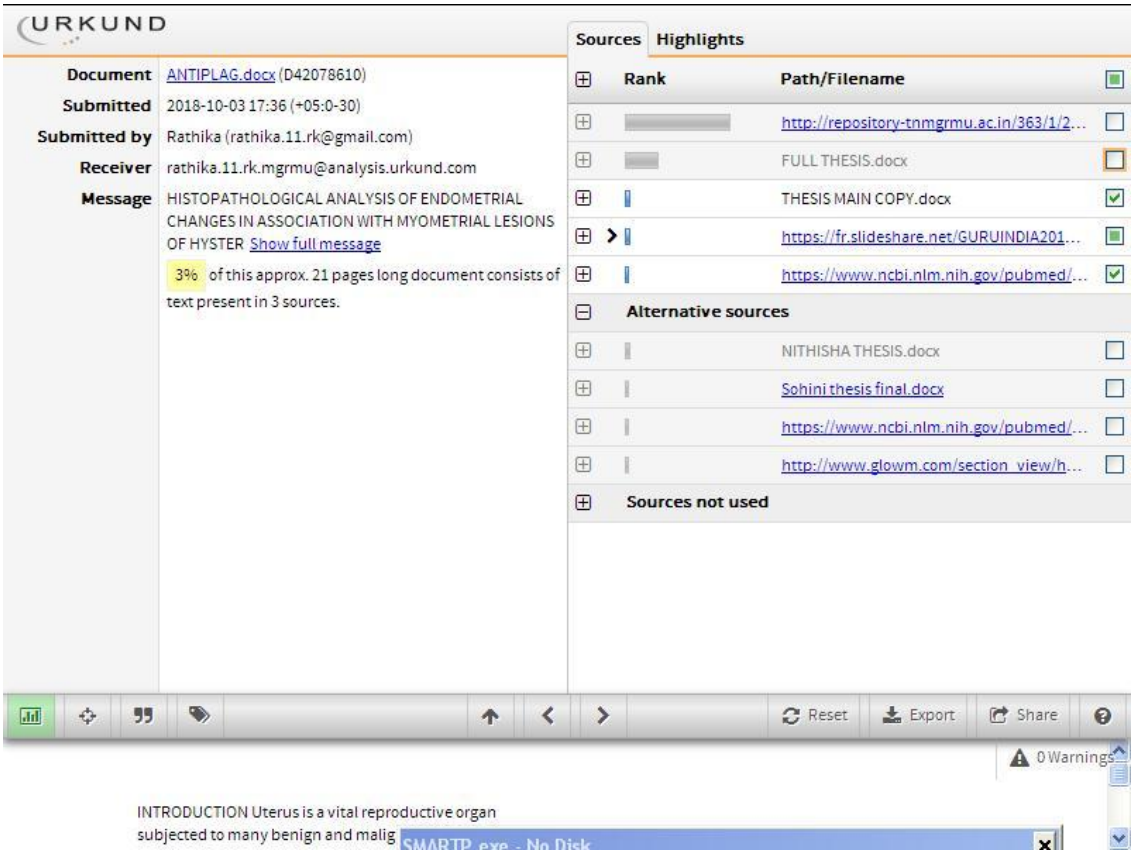
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INSTITUTIONAL ETHICS COMMITTEE
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Date.....

ACKNOWLEDGMENT

It gives me great pleasure and pride to be a post graduate under **Dr.V.Sarada M.D** , Professor and HOD, Department of pathology who has been helping me and guiding me at every stage since genesis of idea for the study. Her valuable suggestions and timely advice were of immense help to me through all stages of this study. She has always been a great moral support and encouragement throughout the conduct of this study and also during my post graduate course. I owe my sincere gratitude to her.

It is my honour and privilege to thank **Dr.K.Ambedkar Raj M.D.,** Professor, Department of Pathology, my guide who at every moment has been a constant source of inspiration throughout my post graduate programme .

I thank our dean **Dr.A.Jesudoss M.S.,D.L.O,** Trichy SRM Medical College Hospital and Research Centre, Trichy for acknowledging the research work.

I thank **Dr. P. Thirumalaikozhundusubramanian M.D**, Vice Principal Trichy SRM Medical College Hospital and Research Centre, Trichy for his encouragement in completing this study.

I thank all my professors, associate professors and assistant professors for their great moral support, constant encouragement, motivation and advice.

I thank my fellow post graduate **Dr V. Bavithra** who has been very supporting and ever encouraging in completing this study.

I thank my family with all my heart for having been a great moral support.

I express my gratitude towards lab technicians and non-teaching staffs of our departments for providing significant support throughout my course.

I sincerely thank all my patients without whom my study would not be possible

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ABBREVIATIONS

- PP - Proliferative Phase
- ES – Early Secretory Phase
- LS – Late Secretory Phase
- DPP – Disordered Proliferative Phase
- SH – Simple Hyperplasia
- CH – Complex Hyperplasia
- A – Atrophic endometrium
- EIN – Endometrial Intraepithelial Neoplasia
- EC – Endometrial Carcinoma
- IM – Intramural
- SM – Submucous
- SS – Subserous
- LMP – Last Menstrual Period
- O – Others
- F – Frequency
- P - Percent

Introduction

INTRODUCTION

Uterus is a vital reproductive organ subjected to many benign and malignant lesions which commonly results from various hormonal imbalances. The myometrium of uterus is composed of bundles of smooth muscle that form the wall of the uterus. The inner cavity of the uterus is lined by the endometrium composed of glands embedded in a cellular stroma[1]. The endometrium is a dynamic tissue that undergoes physiologic and characteristic morphologic changes during the menstrual cycle as a result of the effect of sex steroid hormones like estrogen and progesterone produced in the ovary. A myriad array of compounds has been identified in the endometrium include enzymes, hormones and bioactive peptides.

Normal values for endometrial thickness range from 2 to 16 millimeters, depending on the stage of the menstrual cycle. “Dating” the endometrium by its histologic appearance is often used clinically to assess hormonal status, document ovulation, determine causes of endometrial bleeding and infertility[7]. The cycle begins with the shedding of the upper half to two thirds of the endometrium, referred to as the functionalis, during menses. Under the influence of estrogen, produced by the granulosa cells of the developing follicle in the ovary, the remaining third (basalis) undergoes extremely rapid growth of both glands and stroma.

According to World Health Organization reproductive age group is defined as 15-49 years. The various endometrial lesions including chronic endometritis,

endometrial polyps, hyperplasia and malignancies which present with abnormal uterine bleeding. Adenomyosis is the most common tumor like condition involving the myometrium.It is described as presence of widely-distributed endometrial glands or stromal tissue in the myometrial layer of uterus.

Adenomyosis consists of both epithelial and stromal elements, and is located about 2 to 2.5mm below the endomyometrial junction[1]. Furthermore, leiomyomas are frequently associated with adenomyosis hindering the differential diagnosis. Adenomyosis has been difficult to diagnose without the surgical pathology of a hysterectomy specimen. Uterine leiomyomas account for more than 75% of the benign tumors in women of reproductive age group. Studies have suggested that numerous hormones, growth factors, cytokines and other signal transduction pathways have a role in the pathogenesis of leiomyoma. Estrogen and estrogen-related genes might play a predominant role in the growth rate of leiomyomas. The normal myometrium of uteri expresses higher levels of estrogen receptors which is related to pathogenesis. The leiomyoma is composed of smooth muscle and fibrous tissue and are benign in nature.Based on their location within the uterine wall, leiomyomas are classified into submucosal or subendometrial, intramural or myometrial and subserosal leiomyomas. The latter may be pedunculated and simulate adnexal masses.

Most of the leiomyomas undergo secondary changes in approximately 65% of cases. These include hyaline degeneration (63%), myxoid changes (19%), calcification (8%), cystic changes(4%), and fatty metamorphosis (3%)[1]. The leiomyosarcoma is the malignant counterpart of the leiomyoma and is the most

common pure sarcoma of the uterus. Hysterectomy is the most common gynecological procedure performed for the management of leiomyomas, adenomyosis, abnormal uterine bleeding, endometriosis and utero-vaginal prolapse. Histopathological examination of hysterectomy specimens carries diagnostic and therapeutic significance. Hence this study made an attempt to study the histopathological changes in endometrium with associated myometrial lesions in hysterectomy specimens.

Aims & Objectives

AIMS AND OBJECTIVES

1. To study the changes of endometrium in association with myometrial lesions of hysterectomy specimens with respect to various clinical and morphological features.

2. To analyse the histopathological changes of endometrium in association with myometrial lesions of hysterectomy specimens in our Institution with respect to LMP, age.

3. To assess the age distribution of the myometrial lesions in patients subjected to hysterectomy.

4. To assess the endometrial changes in relation with the types and sites of myometrial lesions in hysterectomy specimens.

Review of Literature

HISTORICAL REVIEW

EMBRYOLOGY AND HISTOGENESIS

The genito urinary system is developed from the urogenital ridge after 21st day of fertilization[1]. The end term of embryo forms the primitive gut which is attached to the posterior wall of the body cavity by a mesentery. On either side of the mesentery, the posterior wall is made up of intraembryonic mesoderm. Urogenital ridge mullerian ducts develops from the lateral side of this inter mediate cell mass [1]. This forms the most of the female genital tract on the mesonephros.This happens by the invagination of coelemic epithelium. By the 8th week they grow caudally and cross entering to the wolffian duct and the gubernaculums.They fuse in the mid line and end at the roof of the urogenital sinus form an elevation called mullerian tubercle. On each side the cranial longitudinal part forms uterine tube and its coelomic opening develops into the fimbrial end[1]. The unfused intermediate part of duct expands and finally fuse to form fundus and the body of the uterus.

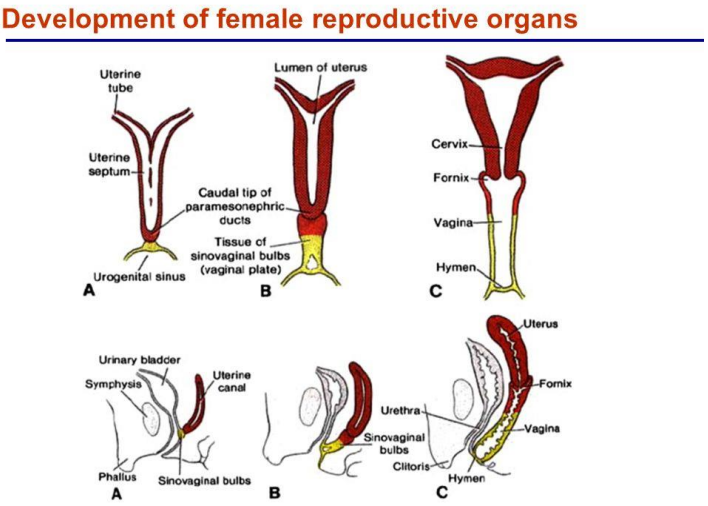


Figure 1 – Development of Female genital system

ANATOMY

The weight of an adult uterus is about 30 to 50 grams on average. These measurements are subjected to individual variations. The average length ranges from 5 to 7 cm. Its greatest depth is 3 cm. The body of uterus comprises of an anterior wall, a posterior wall along with fundus and the lateral margins. The narrow triangular space in the body of the uterus is called as endometrial cavity. The interior limit of the fundus is the base of the triangle while the angle lies at the internal os of the cervix[1,42]. The communication between endometrial cavity and the fallopian tube is through the right and left cornua.

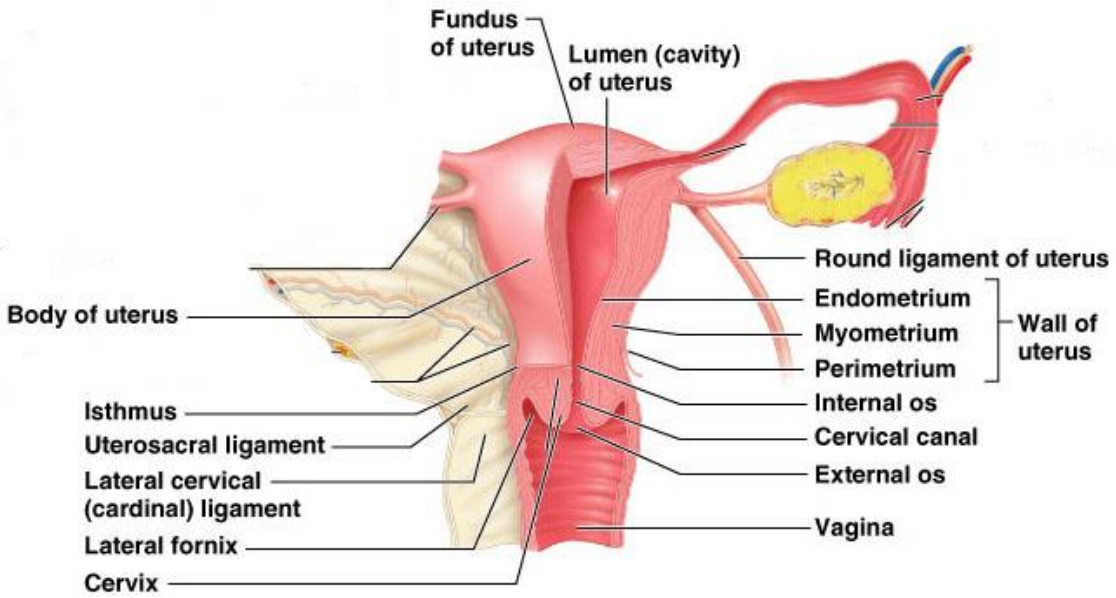


Figure 2 – Anatomy of Uterus

APPLIED HISTOLOGY

The histological architecture of the body of the uterus is characterized by 3 layers. They are

1. Outer Serosal layer

2. Middle Myometrial layer
3. Inner Endometrial layer

The serosal layer extends to point of peritoneal reflection and is identical with the peritoneum[1], [43].The myometrium is composed of fibres that are arranged in interlacing bundles between the strands of interstitial connective tissue. The endometrium is made up of glands and stroma.It is divided into deeply seated basal layer and superficial functional layer.The basal layer is equivalent of reserve cell layer and is responsible for regeneration of endometrium following menstruation.The functional layer is subdivided into the compactum and spongiosum.Characteristic changes take place in the endometrium during the different stages of menstrual cycle [1,34].

HISTOLOGY OF ENDOMETRIUM

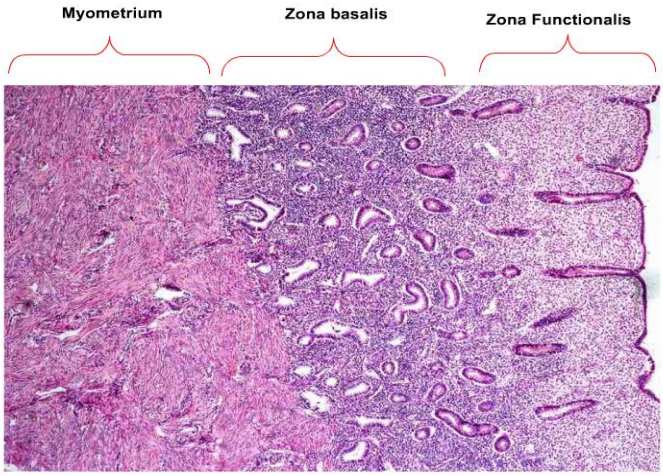


Figure 3 – Histology of Endometrium

Endometrium is composed of two layers. They are stratum basalis which is the basal thin layer and stratum functionalis, the superficial thick layer. These

layers are formed by glands that are held together by connective tissue called as endometrial stroma. The stroma consists of embryonic type highly cellular connective tissue composed of blood vessels and nerves. The two layers of endometrium are distinguished by the arrangement of blood vessels. The stratum functionalis is shed during menstruation and stratum basalis is permanent [1,23]. The arteries from the arcuate -> radial -> straight artery enter into the basal layer. As they progress more apically they becomes tortuous and finally gives off numerous branches. The capillaries end in capillary bed that includes lacunae which are thin walled dilated segments present at the superficial portion of stratum functionalis. (Ross et al, 1995). The surface epithelium is less responsive to hormonal stimuli whereas the functionalis layer is more responsive to hormonal stimuli [1,39].

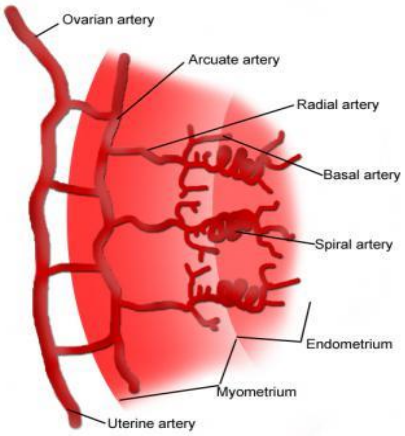


Figure 4 – Blood supply to Uterus.

THE GLANDULAR EPITHELIUM

The glandular epithelium is a single layer of columnar epithelial cells. Their height varies depending upon the functional state ranging from 6µ postmenstrual to 20µ at the end of proliferative phase[2,43]. During the proliferative

phase, the glandular cells have enlarged nuclei and dense chromatin. Between the 10th and 16th day of the menstrual cycle, their DNA content reaches to its maximum (Voker, 1951). During the secretory phase, the nuclei becomes round and vesicular. The nuclei have abundant RNA. After ovulation, the RNA content of the cytoplasm reaches its greatest concentration. The nucleoli of early proliferative phase are finely granular and compact[2,29]. They enlarge as midcycle is approached and reach 2.8μ in diameter (Fassake et al, 1965). During the first week of the secretory phase, the nucleoli has a characteristic tubular or meshwork like structure and the nucleolar channel system which is embedded in an electron dense matrix and contains RNA[2,42]. It serves the exchange of protein between nucleolus and cytoplasm for enzyme synthesis (Dubauszky and Pohlmann, 1960, Armstrong et al, 1973). This channel system apparently occurs only in the human endometrium and seems to depend on adequate levels of progesterone[2,42]. It can be demonstrated by electron microscopy shortly before ovulation.

During the proliferative phase, the cytoplasm is unusually rich in RNA content and is demonstrated by the histochemical techniques (Wislocki and Dempsey, 1945) or by fluorescence microscopy (Dallenbach and Dallenbach – Hellweg, 1968). The cytoplasm of the basal part of the cell contains abundant ribosomes (Borell et al, 1959), bundles of tonofilaments each about 100μ diameter appear around the 13th day of the menstrual cycle under the influence of increased estrogen stimulation[3,9]. They stabilize the rigidity of cells prior to nidation (Clyman et al, 1982). With the onset of secretory phase, the mitochondria multiply and enlarge at the base of the cell near the first aggregate of glycogen. Then,

abundant basal secretory granules collect around smooth endoplasmic reticulum[3,29]. As glycogen, mucopolysaccharides and proteins also accumulate at the lower pole of the nucleus to form cloudy or granular deposits. The large mitochondria nearby swells to giant size and may reach 7μ in diameter. On the 17th day of the menstrual cycle, glycogen is found scattered throughout the cytoplasm[3,43.] With the onset of secretion on 19th and 20th day of menstrual cycle, the cytoplasm along the luminal surface sends out enlarged microvilli filled with secretory products[3,9]. Thereafter the apical portion of the cell is discharged into the lumen. Thus, the epithelial cell expels their products by apocrine secretion and thereby becomes smaller. The glycogen is thought to serve a complex function involving more than pure glandular secretion (Sakuma, 1970).

Sometimes ciliated columnar cells are found among the glandular epithelial cell (Mandl, 1911). These ciliated cells initially lie against the basement membrane. Because of their abundant translucent cytoplasm they can be readily recognized as a "clear cell". The rounded nucleus of the clear cells are generally located above those of the neighbouring epithelial cells (Feyrter and Froewis, 1949). 'Clear cells' are possibly the precursor cells in the proliferative phase and in cystic glandular hyperplasia. Around midcycle of the cycle and in endometrial hyperplasia, there are numerous fully developed ciliated cells. (Maddi and Papanicolaou, 1961).

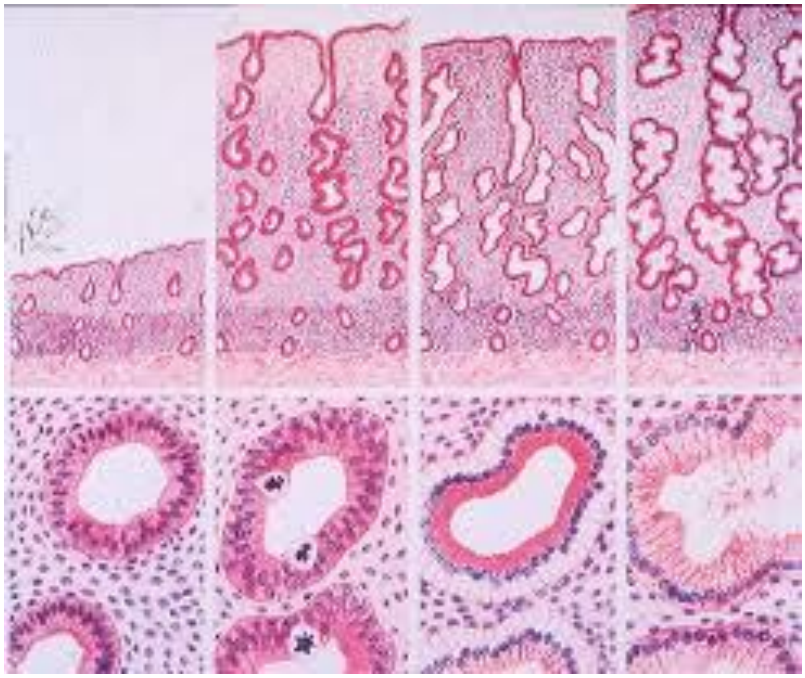


Figure 5 – Glandular epithelium

THE SURFACE EPITHELIUM

During the proliferative phase, the superficial epithelium closely resembles the glandular epithelium although it contains greater number of ciliated cells (Ferenczy et al, 1972). Glycogen appears in large amounts earlier and remains longer than in glandular epithelium. The superficial epithelium differs from glandular epithelium functionally [3,38]. The secretion of surface epithelium is important for the adherence and implantation of blastocyst. Scanning Electron Microscopy reveals the accumulation of the ciliated cells around the mouths of the glands [3,7](Hafez et al, 1975). During the secretory phase, these cilia degenerate. The size and number of their microvilli decrease as the apical surface of the cell continues to bulge into the uterine cavity [3,9].

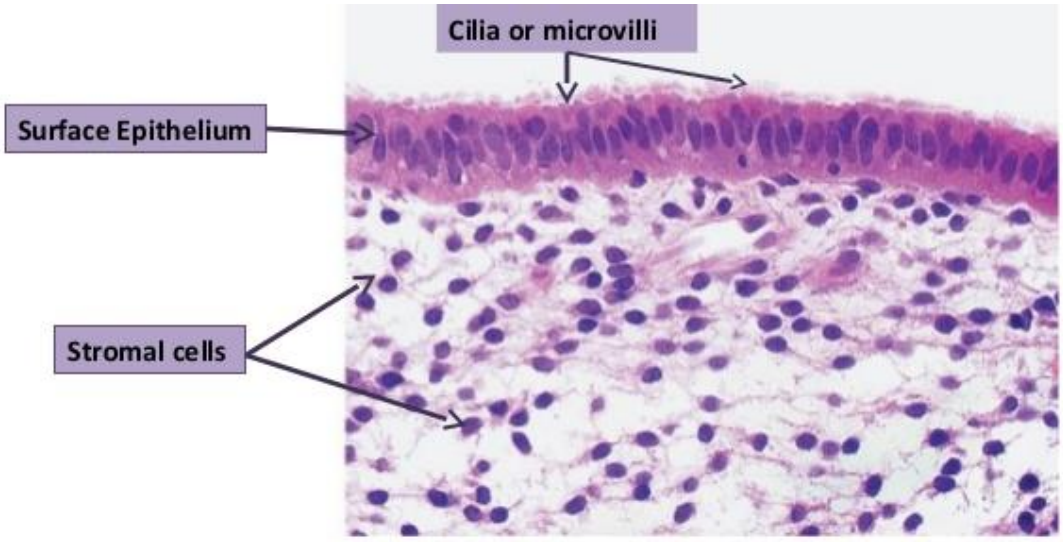


Figure 6 – Surface epithelium and stroma

THE STROMAL CELLS

The endometrial stroma consists of pluripotent mesenchymal cells which are uniformly spindle shaped, poorly differentiated at the beginning of the menstrual cycle. They are joined to one another by cytoplasmic processes. The cells are anchored firmly within a delicate network of reticulin fibers. They have elongated nuclei with abundant chromatin. At the beginning of the menstrual cycle, the cytoplasm of these cells forms a narrow rim around the dark nuclei. The nuclear substance becomes less dense, the nucleoli grow larger and more conspicuous and the nuclear membrane becomes wrinkled at the end of the proliferative phase. There is accumulation of RNA in the cytoplasm of the more superficial stromal cells. The Golgi apparatus and mitochondria remains poorly developed[3,9]. The microfibrils of collagen become apparent not only within the cell but also outside of them. Also there is expansion of smooth and rough endoplasmic reticulum (Wetzstein and Wagner, 1960).

During the secretory phase there is increase in number of mitochondria and smooth endoplasmic reticulum and the Golgi apparatus enlarges. Vacuoles and granules start appearing in the expanding and shortened microvilli. The glycogen and glycoproteins are in diffuse and granular form from the 20th day of the cycle onwards[3,7]. This can be demonstrated in the cytoplasm of the stromal cells with the help of electron Microscopic and histochemical methods (Mckay et al, 1956). Some stromal cells contain fine lipid droplets (Aschheim 1915) which are said to appear after estrogen stimulation. The lipid accumulates in large amounts and the stromal cell may reach the size of decidual cells to acquire a foamy appearance[3,9].

By the end of the secretory phase, the endometrial granulocytes accumulates. These cells are smaller than the decidual cells with a crenated nucleus (Nordquist, 1970) and contains relatively large lysosomal granules[31,41] These are originally thought to be derived from the stromal cells (Dallenbach – Hellweg, 1981) and thought to secrete a proteolytic hormone called relaxin (Dallenbach & Dallenbach – Hellweg, 1964). It has now been shown that these endometrial granulocytes are a population of large granular lymphocytes which are probably derived from the bone marrow and have characteristics of natural killer cells (Bulmer et al, 1987). They play a important role in successful implantation and placentation [1] (Ritson and Blumer, 1987). These cells contain phloxinophilic granules in the cytoplasm (Hamperl, 1954, Hellweg, 1954). These cells are also called as stromal granulocytes or endometrial granulated lymphocytes. They show CD59 & CD69 positivity[3,24,30].

OTHER CELLS IN ENDOMETRIUM

In non-inflamed endometrium lymphocytes appear frequently. Lymphoid follicle formation in the endometrium is not unusual (Monch, 1918). Histiocytes and mast cells are also found in the endometrium. Plasma cells and eosinophils are found very rarely (Feyrter, 1957).

THE RETICULIN FIBRES

The distribution of reticulin fibres varies in the endometrium. The stroma of the basalis and the isthmic mucosa remains uniformly dense. The fibre content of the functionalis layer fluctuates during the menstrual cycle (Hormann, 1908, Hoffmeister and Schulz, 1961). During the first 8 days of the proliferative phase, only occasional delicate reticulin fibres are seen with the light microscopy. Once ovulation approaches, these fibres become denser and thicker. By the 4^{th} week of the menstrual cycle, the fibres enmesh each predecidual cell and form a dense network around the glands and the spiral arterioles. When the progesterone decreases, there is disintegration of reticulin fibres[3,29]. As a result the glands separate from stroma and stromal cells dissociate from one another. The functional state of endometrium can be evaluated from the appearance and quality of reticulum network (Vaczy and Scipiades, 1949).

THE GROUND SUBSTANCE

The ground substance of the endometrium bathes the cellular and fibrous components of endometrium. It chiefly contains high molecular neutral and acid mucopolysaccharides in the early and mid proliferative phase of the cycle. The ground substances begin to resolve into subgroups of low molecular size in the

late proliferative phase. It appears oedematous as the time of implantation approaches in the midsecretory phase. High molecular, neutral and acid mucopolysaccharides reaccumulate in the compacta and around the spiral arterioles during 4th week of menstrual cycle. These changes are essential for the implantation of blastocyst.

THE VESSELS

The vessels of the stratum functionalis differ from the blood vessels of other organ and tissues by their sensitivity to hormones, their unique structure and their ability to respond quickly to such stimuli (Ramsey, 1955, Nieminen, 1962). In contrast, the vessels of the stratum basalis are influenced only little by hormonal changes of the cycle. At the end of proliferative phase, the spiral arterioles of the stratum functionalis that branch from the arteries of the basalis finally attains the upper portion of the endometrium. Progesterone stimulates these vessels to grow larger and longer imparting tortuosity. These changes are especially evident when the ratio of the height of endometrium to the length of the spiral arteries is 1:15 during the second half of the secretory phase (Markee, 1950). The arteries undergo extensive spiraling because they grow at faster rate when compared to the endometrium. Their wall which is thin in the early proliferative phase grows progressively thicker (Wiegand, 1930, Farrer – Brown et al, 1970). The lining endothelial cells which are originally flat now swells and soon contain large, vesicular nuclei (Keller, 1911). The capillaries of the functionalis also respond to harmonal variations. Just beneath superficial epithelium, they branch and pass and becomes the largest in premenstrual phase and in decidua of pregnancy. They form

a lacuna like sinusoids which are called as anastomosing lacuna of Schmidt - Matthiesen (Schmidt – Matthiesen, 1962).

The veins of stratum functionalis also respond to the hormonal stimuli of secretory phase, as other vessels (Küstermann, 1930). The venous network of the endometrium is strikingly dense. Beneath the superficial epithelium, they form thin walled "lakes"[3].

PHYSIOLOGICAL ACTION OF HORMONES ON ENDOMETRIUM

Though Andreas Vesalius in 1545 explained about the pituitary and hypothalamus relationship, only in 1947 Green and Harris together recognized it as a neurovascular complex[3,7]. The gonadotrophin hormones are discovered by Ascheim and Zondek in 1927.In 1931, Fevold, Hisaw and Leonard described the FSH and LH. But the normal physiological sequence of events in menstrual cycle in relation to pituitary and ovary was described only in 1971 by Speroff, Van de wiele and Newton et al. Later on, in 1973 Fraser et al found irregular menstrual cycles are due to FSH & LH deficiency[3,35].

HORMONAL CONTROL OF OVULATION

Ovulation depends upon complex interrelationship between hypothalamus, pituitary and ovary. The gonadotrophin releasing hormones (FSH / LH – RH) that are carried in the hypophyseal vessels to the anterior pituitary, stimulates the synthesis and release of FSH and LH into the general circulation. These hormones are necessary for the growth of the follicles and maturation in the ovary[4,35].

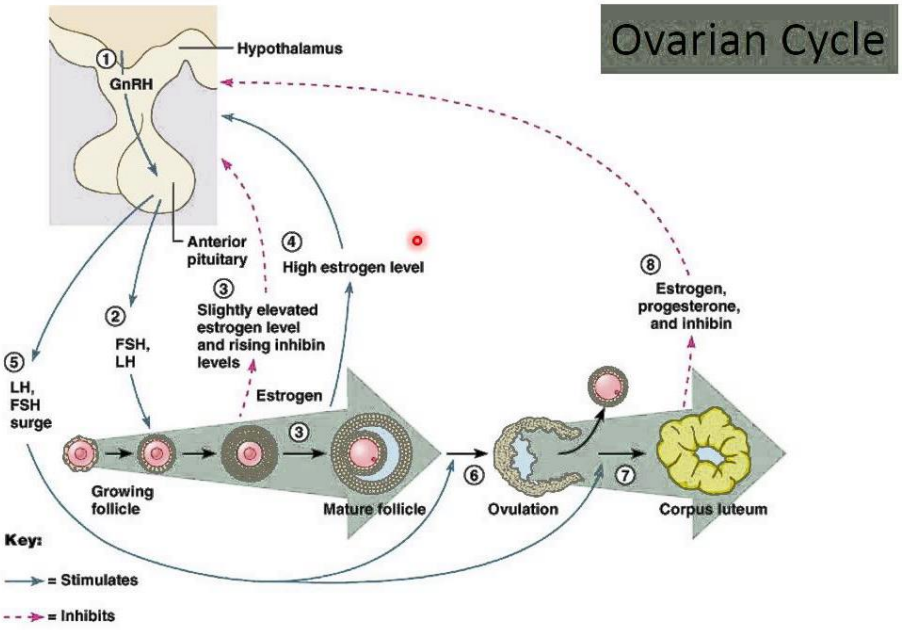


Figure 6 – Hypothalamus – Pituitary Axis

During the midcycle, there is an additional surge of LH release which causes the FSH primed follicle to rupture and the release of ovum. The ruptured follicle is then transformed into corpus luteum which synthesizes the hormones (progesterone and estrogen). These steroidal hormones of ovary inhibit the stimulation of ovary by gonadotrophin by negative feedback mechanism taking place in Hypothalamo - Pituitary axis. If the fertilization does not occur, the corpus luteum remains transient, involutes, ovarian hormone decreases in quantity and then the menstruation follows. The hypophysis then resumes their function and the cycle repeats itself [4].

HORMONAL LEVELS IN NORMAL MENSTRUAL CYCLE

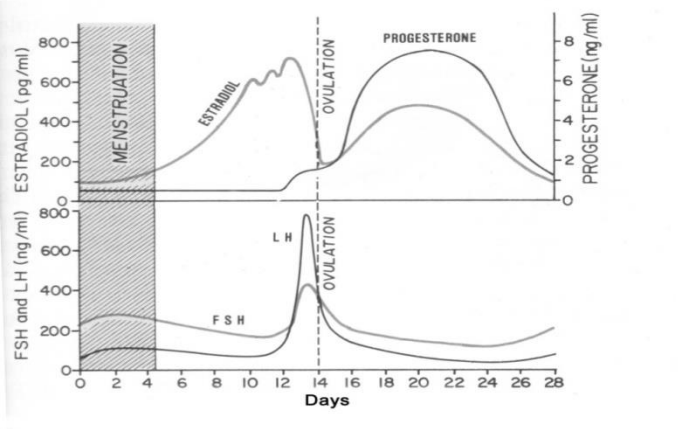


Figure 8 - HORMONAL LEVELS IN NORMAL MENSTRUAL CYCLE

ENDOMETRIAL STEROID RECEPTORS

The steroid hormones trigger their activity through specific receptor sites expressed on the target cells. They are carried from the receptor to the nucleus and to genes to induce the process of transcription and translation resulting in cell proliferation and differentiation[4] (Gorski and Gannon, 1976).

In the stratum functionalis, there is fluctuation of receptors for estrogen and progesterone during the menstrual cycle (Bayard et al, 1978). When the estrogen receptor remains unoccupied by estrogen in the nucleus, it is loosely bound in the monomer state[4,36]. When the estrogen binds, there is activation leading to the formation of a dimer (Scholls, 1984). One aspect of the activation is an increased affinity for estrogen[4]. This increase in affinity is called as positive cooperativity, which increases the ability of the receptors to respond to small changes in the concentration of hormone. The mechanism of action is same in case of progesterone (Edwards et al, 1969). The concentration of estrogen and

progesterone receptors in the fundal region is higher than in the middle and isthmic portion of the uterus [4,18]. The basalis layer has a constant receptor number and the binding is independent of the phase of menstruation[4,12].

The effect of the hormones on epithelial, stromal and endothelial cells is mediated by estrogen receptor (ER) and progesterone receptor (PR).The regulation of EGF receptor content is achieved by secretion of ovarian hormone [4,7] (Ferenczy, 1994). The receptors which are synthesised in the cytoplasm get transported into the nucleus by a dimer of heat shock protein (hsp – 90)[5,18]. With the formation of hormone receptor complex, there is dissociation of hsp – 90. In the early proliferative phase, there is gradual increase in estradiol receptors. The progesterone receptors are fewer in number when compared to estrogen receptor[5,29].

In the late proliferative phase there is increase in the concentration of total estradiol receptors. The cytoplasmic receptors increase greatly in number correlating with the surge of plasma estradiol. After ovulation, the total estradiol receptors decrease rapidly in the early secretory phase[5,18].

ESTROGEN

In contrast to other steroid hormones, even minute amount of estrogen is very potent and is capable of producing rapid, significant changes in the target cells. In endometrium, both stromal and glandular cells respond actively to estrogen. Estrogen regulates the amount of genetic material which are available for transcription resulting in cell proliferation seen as mitosis[4]. The first change in

the glandular and stromal cells of endometrium is the increase in amount of RNA in the nuclei and nucleoli followed by the increase in cytoplasmic RNA (Davidson, 1965). Finally the endometrial cells cease to proliferate with the secretion of progesterone[5].

PROGESTERONE

In the human endometrium the first evidence of effect of progesterone is detectable with the light microscope only after 36 hours. The changes noted are clearing of the nuclei of glandular epithelial cells and appearance of granules of glycogen at the base of the glandular epithelial cells[5,30,32]. In Electron Microscopic studies, giant mitochondria which contains DNA near the glycogen granules are found (Merker et al, 1968). The progesterone stimulates the mitochondria in synthesizing proteins. Later, under the influence of progesterone, a nuclear channel system is developed. There is cessation of mitotic activity. There is production of glycogen, neutral and acid mucoploysaccharides and lipids by the glandular cells. By the 2nd week of the secretory phase, the stromal cells start differentiating into large predecidual cell[5,36].

THE NORMAL MENSTRUAL CYCLE

The first histological description of the cyclical changes in the endometrium was done by Hitschmann and Adler (1908).

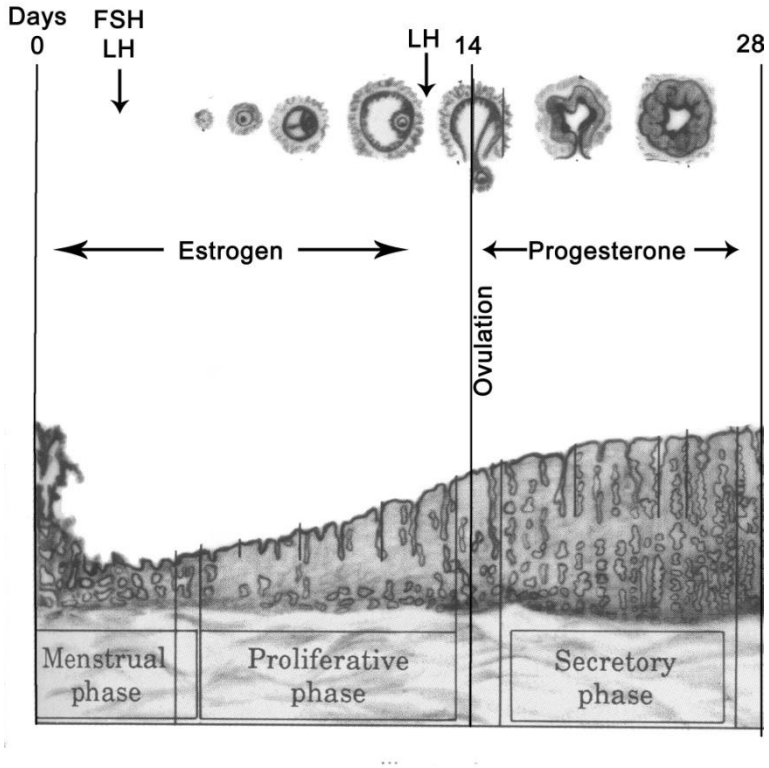


Figure 9 – Normal menstrual cycle

However, Noyes et al in 1950, first described in detail on "dating of endometrium" from histological criteria, that is on how to diagnose how far an endometrium has developed in the menstrual cycle from the characteristic histological changes that occur at specific times. Moricard in 1954 and Philippe et al in 1965 confirmed the data of Noyes et al. The menstrual cycle divided into three phases. They are

1. Proliferative phase
2. Secretory phase and
3. Menstrual phase

PROLIFERATIVE PHASE

The endometrium regenerates from the basal layer and the part of the functionalis layer, which remains after menstruation. The epithelium actively covers the denuded surface. There is no evidence of mitotic activity in the early stages of regeneration. Upon the hormonal stimulus the initial resurfacing occurs independently. The normal proliferation lasts for about a period of two weeks. But there is variation in time taken for the development of follicle from women to women and between cycle to cycle. Therefore, it is impossible to date the proliferative phase with any accuracy and it is divided into 3 phases -early, mid and late proliferative phase. In the early stages, the glands are lined by low columnar epithelial lining measuring 6μ in height and appears as simple tubules. Both in the glands and stroma, there is evidence of mitotic activity. The stroma is loosely packed and composed of spindle cells.

In the mid proliferative phase, there is elongation of glands continue and the stromal edema develops. The elongation of the glands outstrips the stromal edema and consequently the glands acquire tortuousity. In the late proliferative phase, the edematous stroma subsides and the tortuosity of the glands increases. There is maximum mitotic activity in the glands and stroma which corresponds to the preovulation peak of the estrogen. There is pseudostratification of glandular epithelium due to the heaping up of columnar epithelium[14]. The glandular cells measure 20μ in height. There is distension of lumen. Small amount of glycogen vacuoles are found in the cells. As the proliferative phase progresses, nucleoli in the glandular cells become more prominent[6,14]. Over the period, the individual

stromal cells show only little change other than growth and appear to contain little amount of cytoplasm in H & E sections (naked nuclei appearance).

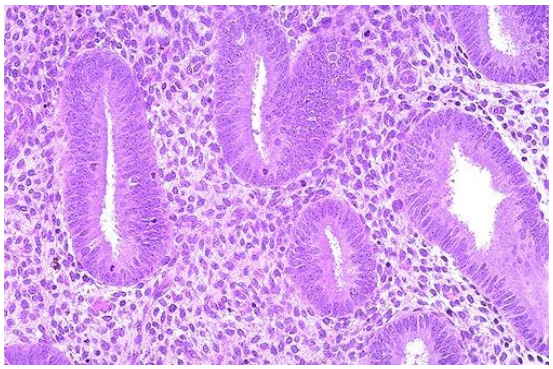


Figure 10 – Proliferative phase

SECRETORY PHASE

Secretory phase is divided in to three phases. They are:

1. Early secretory phase
2. Mid secretory phase and
3. Late secretory phase

In the glandular epithelium, subnuclear vacuolation occurs 36 – 48 hours after ovulation. It is considered as one of the early signs of ovulation when the majority of the cells show subnuclear vacuolation. On 16^{th} -19^{th} day of cycle, the secretions of the subnuclear vacuoles gradually moves to the apical pole of the cells and nucleus takes up a basal position. By the 16^{th} day of cycle, there is loss of glandular pseudostratification. For some 2 – 3 days after ovulation, mitotic activity is still apparent and continues in the glands. The secretions make the cells to lose their dividing ability. Mitosis is absent after 19^{th} day[6]. During ovulation, the epithelial cells express B72 and 32 very late antigens – 1. (Ferenczy, 1994)

The secretions accumulate at the apical poles of the cells and protrude as blunt projections into the gland lumen, becoming pronunced by day 21 of the cycle. As the secretory material is shed by the apocrine method, the epithelial surface assumes irregular shaggy appearance.There is dialation of the gland lumens by the secretory material. Secretory activity continues for several days post ovulation. If pregnancy does not ensue, there is decline in secretory activity after day 22. The secretory activity varies in different parts of endometrium. There is involutional changes of the glands and there is inspissation or gradual disappearance of luminal secretions. The glands collapse progressively and papillary tufts of epithelium project into the lumen, giving rise to characteristic saw toothed appearance[7,8].

Thereafter the glands show various degenerative changes with ragged epithelial cell borders along with the appearance of apoptosis and giant autophagocytic lysosomes. During the second half of the secretory phase, typical changes occurs in stroma. If pregnancy has not ensued, there is involution of corpus luteum and there is fall in plasma progesterone levels. The estrogen levels which falls temporarily after ovulation reaches a second peak by the day 21 and 22. The stromal oedema begins apparent during this period of maximal estrogen stimulation. Increase in the level of estrogen is associated with vascular endothelial swelling and increased endothelial capillary lining fenestration[7]. These changes are brought about by Prostaglandin F_2 (PGF2) and Prostaglandin E_2. (Ferenczy, 1980, Smith et al, 1983).

The oedema subsides by 23rd day. There is prominent spiral arteriole. This is because of increase in length of the arterioles. The predecidual changes occurs in the stromal cells immediately adjacent to these vessels. There is enlargement of stromal cells to acquire a polygonal shape with small rounded nuclei. The cytoplasm is copious and there is accumulation of glycogen and lipid. These changes cause the separation of the endometrium. During the last two days of the menstrual cycle prior to menstruation, there is accumulation of granulocytes in the endometrial stroma[7].

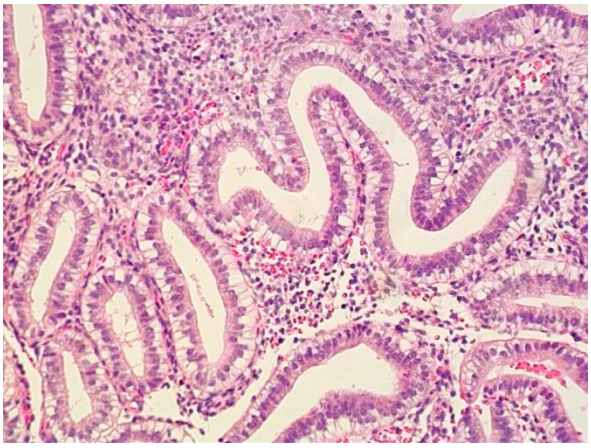


Figure 11- Secretory phase

MENSTRUATION

At the end of each cycle, if pregnancy has not ensued appropriate proportion of the endometrium is shed. Together with blood inspissated, secretory material and other debris makes up the menstrual flow. Usually lasts for some four days. This process is related to the hormonal levels. There is deficiency in both estrogen and progesterone levels in the later stages of the cycle (Zuckerman, 1949). Also the hormones cause fluid loss in the endometrium and it shrinks

(Markee, 1950). Approximately 30% of the bulk is lost. With further reduction in blood flow, this shrinkage causes further coiling of the spiral arterioles. Thus, shrinkage causes the glands become closer and gives an impression of increased cellularity. This is heightened by the endometrial stromal granulocytes and leucocytes accumulating at this stage. Immediately preceding the menstruation , the spiral arteriole constricts by the shrinkage of endometrium along with blanching of the overlying epithelium. It is suggested that reduction in the circulating progesterone-estrogen concentration below some critical level triggers the effect on spiral arterioles (Zuckerman, 1949 loc cit). In due course of time, these vessels dilate and the damaged vessel wall enables the erythrocytes to pass through. As a result of this, small haematoma is formed beneath the surface, raising blebs. The blood comes to lie directly on the surface when the necrotic epithelium is shed. Thus, the shedding of endometrium starts superficially and proceeds to the deeper layers following which rapid disintegration occurs. The endometrium is usually shed in a piecemeal fashion and occasionally shed in larger fragments. The stroma is heavily infiltrated by acute inflammatory cells[8,9].

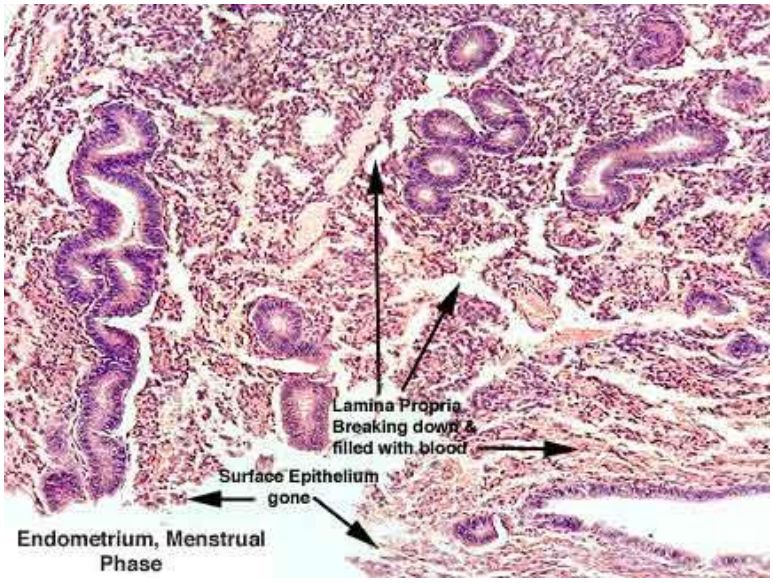


Figure 12 – Menstrual phase

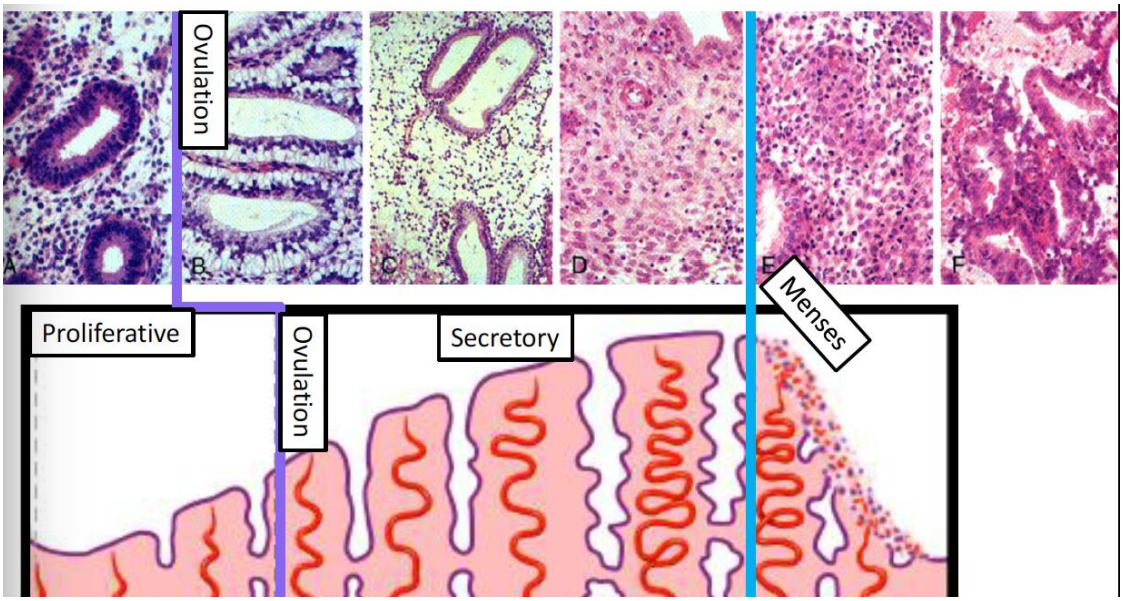


Figure 13 – Summary of cyclical changes

VARIATION IN MENSTRUAL CYCLE

There is considerable variation in length of the cycle in different women. The mean is 29.6 days. There is a tendency for decrement in mean cycle length with age (Treloar et al, 1967). Any menstruation beyond this limit, any bleeding

inbetween the menstrual cycle and any premenopausal acyclical bleeding are considered abnormal. The menstrual bleeding duration also exhibit variation from 2 to 7 days with a mean of 5 days (Guillebaud and Bonnar, 1978). Any menstruation lasting for 8 days or longer is regarded as excessive. The average blood loss in menstruation is about 80ml/cycle (Hallberg et al, 1966). Blood loss more than this is considered abnormal.

DYSFUNCTIONAL UTERINE BLEEDING

The endometrium responds to various alterations in hormonal balance caused due to deficiency of hormone, absence of hormone or excessive hormonal secretion. Alteration in the hormone status occurs either due to intrinsic ovarian abnormalities (primary) or the hypothalamo- pituitary–ovarian axis disturbances (secondary). These hormonal changes brings about arrest in maturation of follicles at different stages resulting in morphological changes. This corresponds to the maturation stage at which the follicles become impaired. Arrest of follicular maturation leads to lack of stimulation of endometrium when the insult occurs during the hormone secreting stages of follicle or corpus luteum. When the insult results in arrest of follicular regression leading to anovulation or preventing the corpus luteal involution the endometrium will be in the state of hyperstimulation[7,8].

Hormonal imbalance occurs due to deficiency of one hormone or excessive amount of other and normal state of one. This imbalance produces changes in the morphology of the endometrium. These changes can be differentiated with

additional factors like clinical history, general examination of patient and the diagnosis is made with the microscopic examination of endometrial samples.

Anovulatory disturbances

- Deficient Proliferation
- Endometrial atrophy
- Estrogen Withdrawal bleeding
- Irregular Proliferation[9]

Ovulatory disturbances[9]

a) Deficient Secretory state

1. Deficient Secretory state with dissociated delay
2. Deficient Secretory state with co-ordinated delay
   - Apparent delay
   - True delay

b) Progesterone receptor deficiency

1. Dysmenorrhoea Membranacea
2. Irregular shedding

ANOVULATORY DISTURBANCES[9]

DEFICIENT PROLIFERATION

Due to central hypogonadotrophism or damage to ovary, if a growing follicle does not attain maturity, only very little amount of estrogen will be produced with two consequences.

1. The LH peak will not occur and LH levels remains low because of insufficiency of feedback stimulation.This is due to the decreased concentration of FSH in the early phase. Thus, ovulation does not take place[9].
2. The endometrium will not undergo proliferation in a right manner because it is understimulated.Though the concentration of LH is too low to induce ovulation, it may cause sporadic luteinization in the sufficient follicle[9].

Histologically, the endometrial glands and stroma exhibit a distinct growth retardation. The glands are straight and narrow. The lining epithelium of the glands is low columnar and contains chromatin rich nuclei in single row with scant cytoplasm. The content of estrogen receptor is low. Mitotic activity is rare. The stromal cells are small, spindled, poorly differentiated and packed densely. The general height of the endometrium is moderate, with its slightly irregular surface because of growth variations. The regions which are located close to the blood supply are slightly more advanced in their proliferation. This picture remains constant throughout the period of menstrual cycle with little variations. Occasional subnuclear vacuoles may be found indicating focal abortive secretion induced by very little amount of progesterone that are produced in luteinized regions of the insufficient follicle[9].

IRREGULAR PROLIFERATION:

Although a follicle matures normally, ovulation may not take place either because of a defect in LH stimulation or FSH hyperstimulation or because of the ovarian damage. The persistent unruptured follicle will continue in estrogen

production beyond the proliferation phase for a varying number of days. Then it slowly regresses resulting in anovulatory shedding.This may occur at the same time of menstrual shedding or may be more or less delayed in onset depending upon persistence of the follicle. Irregular proliferation also develops when previous repeated anovulatory cycles have built up a relative estrogen predominance that increases with each successive anovulatory cycle.

Histologically, the growth of the glands and stroma is greater than that of the normal proliferative phase. The glands vary in their distribution.They appear either closely packed or widely dispersed and there is difference in their diameters. Some may be lined by a pseudostratified or even stratified tall columnar epithelial cells. On immunohistochemical staining, the nuclei of proliferating epithelial cell exhibit strong positivity for estrogen receptors. The stroma is irregularly edematous and is composed of densely packed spindle cells. The spiral arteriole remains underdeveloped. Instead thin walled venules appear. Although there is variation in the height of the endometrium, it is usually markedly increased[9].

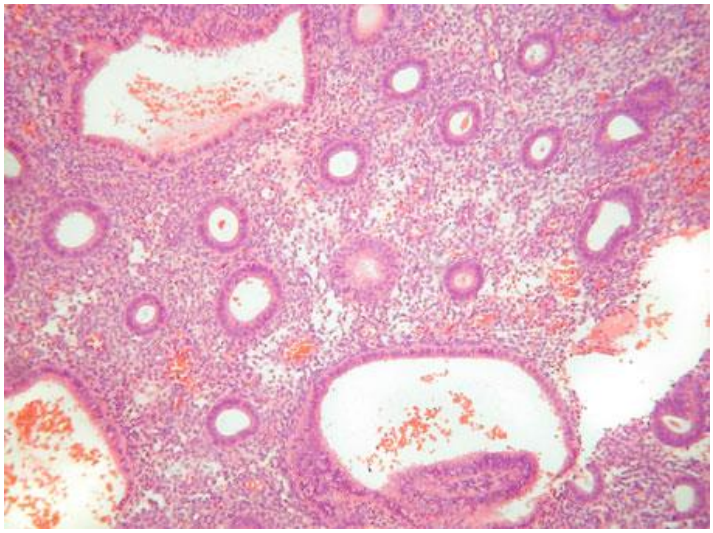


Figure 14 – Irregular proliferation of endometrium

If the ovulation occurs, the basal vacuoles are seen in the highly proliferating glands which lie close to the blood supply. In such cases, a delayed and deficient secretion occurs that is never developed as fully as in a normal menstrual cycle. In instance, sporadic luteinisation occurs in part of the granulosa cells of the persistent unruptured follicle in a similar manner as in the insufficient follicle. These luteinized cells also produce little amount of progesterone which can induce abortive secretion with the appearance of small basal vacuoles in the glandular epithelium. These can be differentiated from those of a truly delayed ovulation by their scanty number and small size. If there is unopposed stimulation of estrogen, then the irregular proliferation gradually progresses to atypical hyperplasia or to a simple (Cystic) glandular hyperplasia[9].

ENDOMETRIAL ATROPHY

During the reproductive age, atrophy of endometrium is always abnormal and it indicates a complete absence of response of endometrium to the ovarian hormones. This may be caused either by primary absence or surgical resection of ovaries or chemical toxins causing severe damage to the hypothalamic pituitary centre or by the local refractoriness of the endometrium to the ovarian hormones. The endometrial refractoriness is usually associated with normal ovarian function and a regular biphasic menstrual cycle (Plotz, 1950; Eufinger 1952) and is termed as the ‘silent ovulation’ of Stieve (1952). This condition is caused due to the inability of the cells of the endometrium to produce hormone receptors. If either the hormone or the receptor is unavailable, cellular proliferation and differentiation does not take place[10].

Histologically, the epithelial and stromal cells are smaller even at higher magnification. Glands resembles capillaries and can hardly be distinguished under lower magnification. They are very sparsely distributed and are lined by low cuboidal cells with small, round nuclei and dense chromatin. The cytoplasm is scant and no mitosis is noted. The stroma is composed of small, densely packed spindle cells. The entire height of endometrium is reduced very much and the stratum basalis is hard to be recognized. In extreme instances, no glands are noted and the flat surface epithelium is separated from the myometrium by a stromal layer of few cell thickness. There is minimal blood supply and no spiral arterioles are made out. The endometrial atrophy is sometimes associated with the development of large dilated venules situated superficially beneath a thin endometrium. These venules may rupture sometimes and are probably remains the cause of uterine bleeding[10].

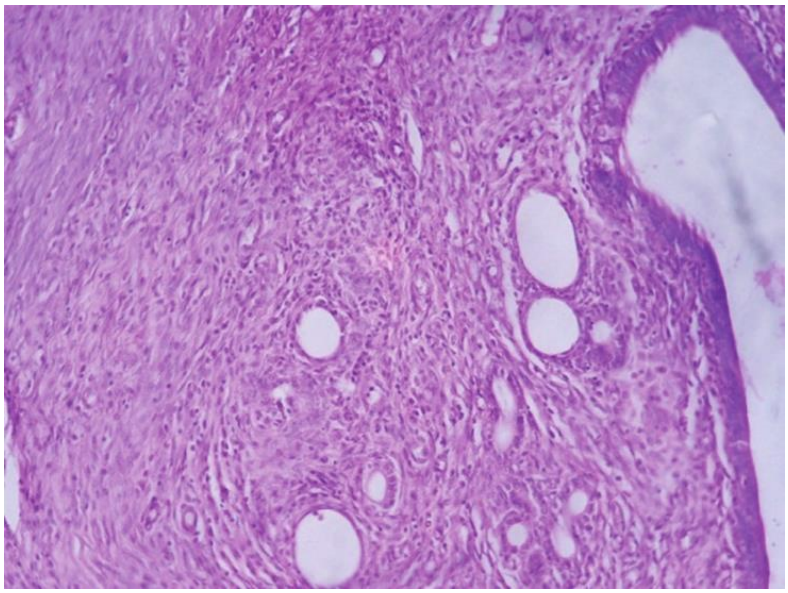


Figure 15 – Atrophic endometrium

OVULATORY DISTURBANCES

THE DEFICIENT SECRETORY PHASE

This entity encompasses a variety of disturbances in the function of corpus luteum either of central or ovarian origin with or without preceding abnormal follicular development. Some of these syndromes are precisely recognized morphologically as they specifically produce changes in the structure of endometrium[11].

The stimulatory effect of progesterone on the endometrium becomes deficient when the hormonal balance shift in favour of estrogen the progesterone deficiency can be absolute when the production or secretion of progesterone is suppressed or relative when hyperestrogenism develops. An absolute progesterone deficiency may occur after normal ovulation if the corpus luteum fails to develop normally or regress too quickly because of a central or ovarian defect such as inadequate luteinization of the granulosa cells or by suppression of progesterone release by elevated prolactin levels (Tubert, 1978) or an ovarian defect in the ability to induce follicular development (Fox & Buckley, 1982).

A relative progesterone deficiency may follow a preceeding follicular persistence with delayed ovulation. The associated secretory phase is of normal duration or may show an early breakdown. In other instances, the corpus luteal insufficiency is preceded by an impaired development of follicle with inadequate stimulation of the granulosa cells which may be caused by insufficient secretion of FSH in the early follicular phase. In these circumstances, progesterone could not fully act on the deficiently proliferated endometrium. Further, the luteal phase

is not only deficient but truly or apparently shortened (Strott et al, 1970, Jones, 1973 and 1975, and Sherman and Korenman, 1974). An apparently luteal phase of short duration may result from early ovulation after a phase of short and deficient proliferation. On the other hand, the secretory phase may either be truly delayed after normal ovulation or apparently delayed following delay in ovulation[11].

In most of the conditions, the concentration of plasma progesterone are low during the luteal phase (Moszkowski et al 1962, Abraham et al, 1974). Rarely a defect of progesterone receptors in the endometrium may be the cause for a relative deficiency of progesterone in the presence of a normal functioning corpus luteum (Laatikainen et al, 1983). Proper and correct evaluation of the patient requires endometrial biopsy from at least two consecutive cycles (Jones et al, 1974). On the application of strict criteria, a deficient secretory phase due to endogenous disturbances appears to be more common than the previously assumed one although Israel in 1959 reported it in only 3.5% of his infertile patient and Sillo – Seidle and Dallenbach – Hellweg in 1974 found it in the 20% of their infertile patients. The deficient secretory phase is divided into two types, each with different cause (Gigon et al, 1970)

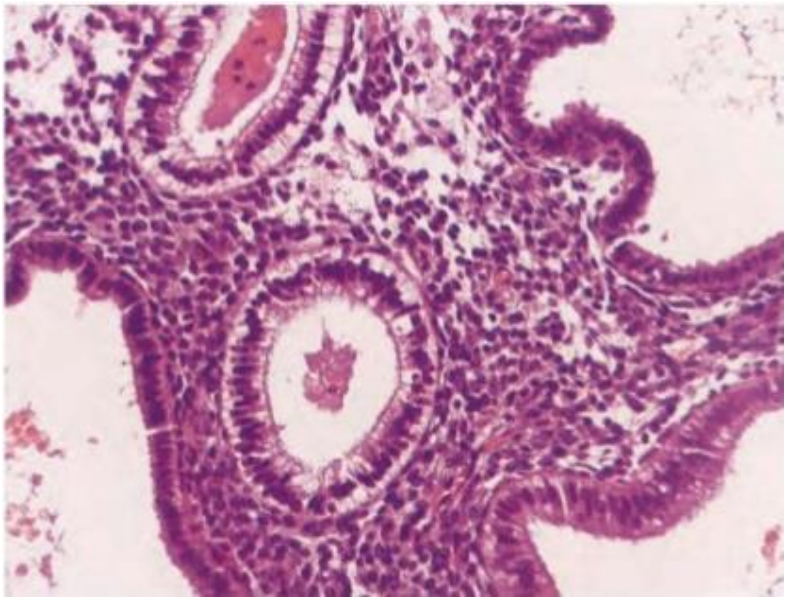


Figure 16 - DEFICIENT SECRETORY PHASE

PROGESTERONE RECEPTOR DEFICIENCY

A deficient secretory phase is found in women with a normally functioning corpus luteum and a properly timed ovulation (Laatikainen et al, 1983 loc cit and Spirtos et al, 1985). These patients have progesterone receptors deficiency and consequently not only endogenous progesterone (Cooke et al, 1972), but also progesterone therapy has null effect on the endometrium.

ENDOMETRIAL HYPERPLASIA (STANLEY J. ROBBOY ET AL)

The endometrial hyperplasia is a heterogeneous group of disorders of proliferation. A confusing multiplicity of descriptive terms and a variety of largely unsatisfactory classification system hinder a full understanding of the nature of hyperplasia. The hallmark of hyperplasia is an increased glandular to stromal ratio with associated architectural and sometimes cytological changes[11].

The International Society of Gynecological Pathologists (ISGP) and the World Health Organization (WHO) proposed a classification scheme in which architectural and cytological features are evaluated independently and this classification is now widely accepted. This classification divides the lesions into those that have cytological atypia and those that do not, the architectural pattern, which is simple or complex is of secondary importance[11].

W.H.O. CLASSIFICATION OF ENDOMETRIAL HYPERPLASIA

Endometrial Hyperplasia

- Simple
- Complex (adenomatous)

Atypical Endometrial Hyperplasia

- Simple
- Complex (adenomatous)

ETIOLOGY

Endometrial hyperplasia occurs as a result of excessive stimulation by estrogens.

HISTOLOGICAL FEATURES OF SIMPLE HYERPLASIA

General

Increased gland:stroma ratio (greater than 1:1)

Diffuse changes throughout endometrium

Glands

Architectural features

- Variation in size and shape of glands
- Small to large and cystically dilated
- Minimal and focal crowding
- Minimal branching with outpouchings and infoldings
- No complex angularity

Cellular features

- Abundant and cellular epithelium
- Ciliated cell change common
- Pseudostratification

Nuclear features

- Oval and elongated
- No significant variation in size or shape
- Evenly dispersed chromatin
- Small, inconspicuous nucleoli
- Variable mitotic activity

Stroma

- Abundant and cellular
- Small, oval cells with scanty cytoplasm
- Mitotic activity in stroma
- Prominent superficial venules
- Inconspicuous spiral arterioles[11]

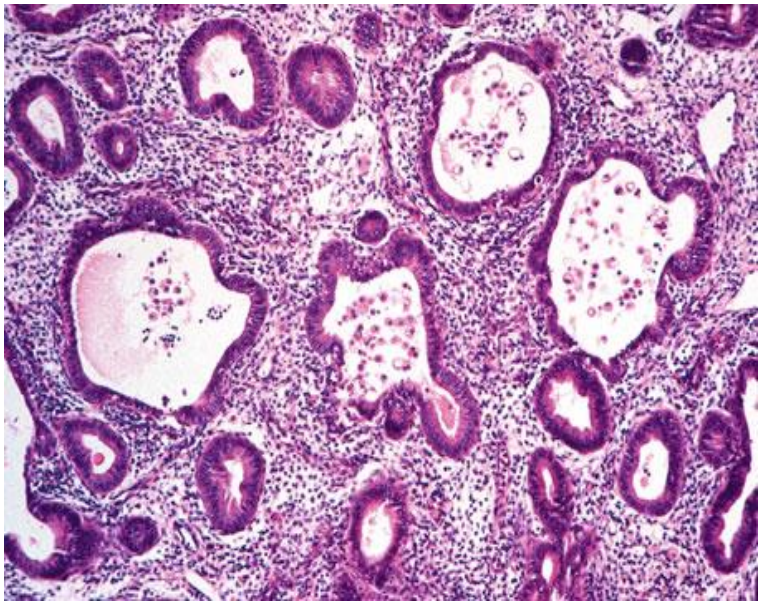


Figure 17 – Simple hyperplasia without atypia

HISTOLOGICAL FEATURES OF COMPLEX HYPERPLASIA[11]

General

- Focal to extensive
- Greatly increased gland:stroma ratio (greater than 3:1)

Glands

Architectural features

- Marked variation in size and shape
- Marked crowding
- Branching with papillary infoldings and outpouchings(budding)
- Complex angularity

Cellular features

- Abundant and cellular epithelium
- Ciliated cell change (less than in simple hyperplasia)

- Squamous change
- Pseudostratification

Nuclear features

- Oval and elongated
- No significant variation in size or shape
- Evenly dispersed chromatin
- Small, inconspicuous nucleoli
- Variable mitotic activity

Stroma

- Scanty and inconspicuous
- Dense and cellular

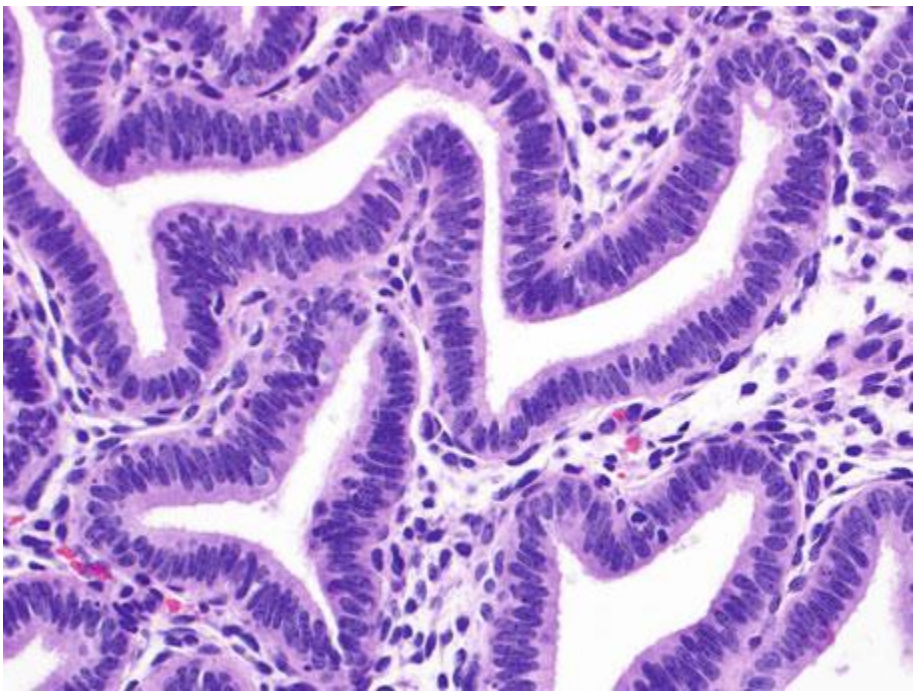


Figure 18- Complex hyperplasia without atypia

HISTOLOGICAL FEATURES OF SIMPLE ATYPICAL HYPERPLASIA

General [11]

- Architectural changes are diffuse throughout endometrium
- Cellular changes are focal to diffuse
- Increased gland:stroma ratio (greater than 1:1)

Glands

- Architectural features
- Variation in size and shape
- Small to large and cystically dilated
- Minimal and focal crowding
- Minimal branching with infoldings and outpouchings
- No complex angularity

Cellular features

- Abundant and cellular epithelium
- Ciliated cell change common
- Pseudostratification
- Dense eosinophilia

Nuclear features

- Elliptical to round
- Variation in shape and size
- Hyperchromasia
- Nucleoli - prominent, enlarged and irregular

- Coarse clumping of chromatin
- Vesicular nucleus →hypochromasia
- Variable mitotic activity

Stroma

- Abundant and cellular
- Small, oval cells with scanty cytoplasm
- Mitotic activity in stroma
- Prominent superficial venules
- Inconspicuous spiral arterioles

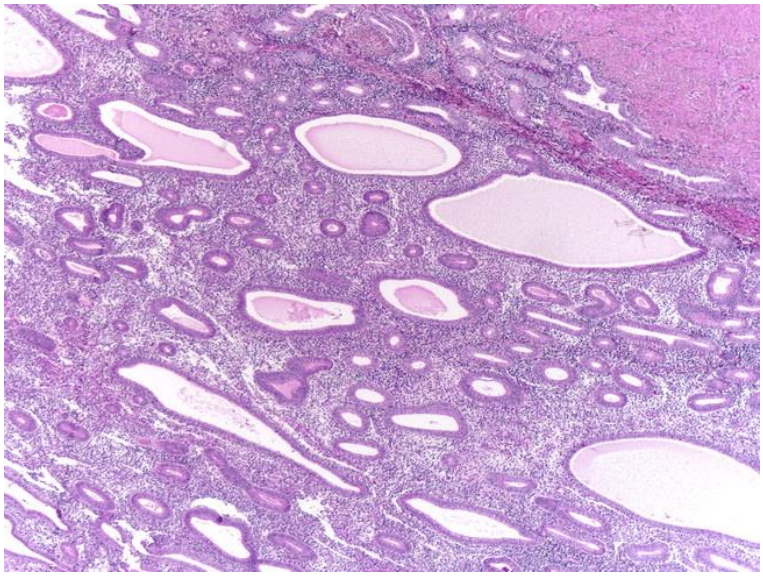


Figure 19 – Simple hyperplasia with atypia

HISTOLOGICAL FEATURES OF COMPLEX ATYPICAL HYPERPLASIA[11]

General

- Focal to extensive
- Greatly increased gland:stroma ratio(greater than 3:1)

Glands

Architectural features

- Marked variation in size and shape
- Marked crowding
- Branching with papillary infoldings and outpouchings
- Complex angularity

Cellular features

- Abundant and cellular epithelium
- Ciliated cell change (less than in simple hyperplasia)
- Squamous change
- Pseudostratification
- Dense eosinophilia

Nuclear features

- Elliptical to round
- Variation in shape
- Variation in size
- Hyperchromasia
- Nucleoli prominent, enlarged and irregular
- Coarse clumping of chromatin
- Vesicular nucleus→hyperchromasia
- Variable mitotic activity

Stroma

- Scanty and inconspicuous
- Dense and cellular[11]

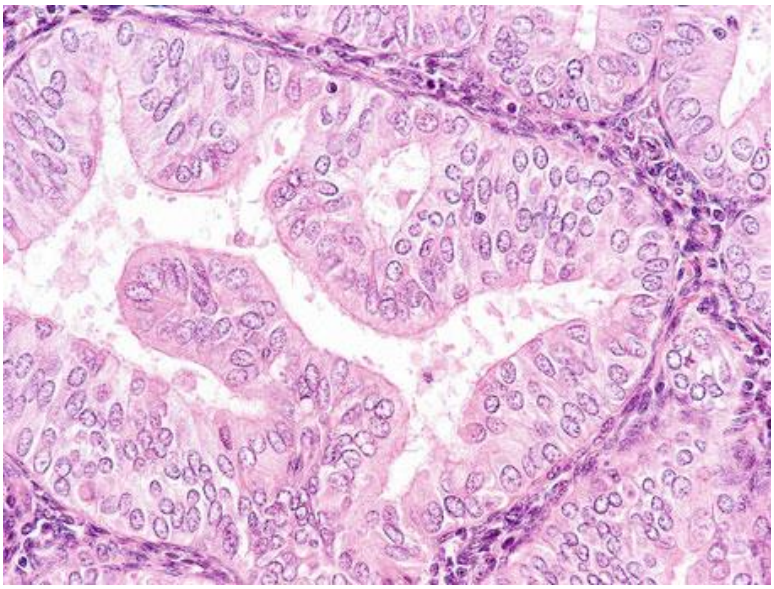


Figure 20 – Complex hyperplasia with atypia

LEIOMYOMA (FIBROID)

Leiomyoma is the most common tumor of uterus and that of female pelvis. It is the most common cause of hysterectomy worldwide. 52 percentage autopsy studies have shown that approximately 20% woman over 30 years of age harbor uterine myomas of various sizes (Novak et al)

Leiomyoma is the benign tumor composed mainly of smooth muscle cells but also contains varying amounts of fibrous tissue[11-18].

INCIDENCE

It is difficult to determine the exact incidence of these tumors. They represent 20-30% in the women over 30 years of age, rising to more than 40% in those over 40 years of age [12].

AGE

Leiomyoma occur commonly in women during the period of mid reproductive years. They have also been reported on rare occasion in young girls (augensen-1818). Premenopausal women showed an average number of myoma which is three times higher than in case of post menopausal women[12-18]

RISK FACTORS

Age: As age of menarche decreases, there is an increased incidence of leiomyoma. Post menopausal women have a 70-90% decreased risk

Child bearing: Women having a live born child have a 20-50% decrease in risk. This reduction in risk gradually increases with number of children born. However, the protection offered by childbirth is only temporary because the risk increases when the time for her most recent child birth is increased (Telinde et al)

Exogenous hormones: Exogenous hormones like unopposed estrogen with progestins show an increase in the risk [12-16]

Family history: Positive family history increases the risk upto 3.5 fold [12]

Race: There is 9 fold increase in incidence of leiomyoma among black women (North American clinics)

Diet and other factors: Obesity increases the risk of incidence of fibroids, while cigarette smoking is associated with reduced risk (Parassiini F et al 1988). Myoma is associated with consumption of beef where as high intake of green vegetable seems to have a protective effect (Chiaffasino F etal 1999). Low physical activity, high mental stress were one of the risk factors in the etiology and pathogenesis of this disease.

ETIOLOGY

Uterine leiomyoma was first believed to be purely a local growth due to the local reason. But by the end of 19th century, it was accepted that myoma of the uterus was related to hormonal disturbances[13]. In 1935, Witherspoon described 3 pathological changes that were etiologically closely related.

1. Myoma of Uterus.
2. Microcystic degeneration of ovary with incomplete leutinization.
3. Cystic glandular hyperplasia of the endometrium (J clinic path 1970).

It is said that hormones especially estrogen, growth hormones and progesterone play a vital role in the development and maintenance of uterine leiomyoma. Faber et al in 1972 and Tamaya et al in 1978 found that the smooth muscle cells are sometimes increased in woman with leiomyoma in their study. In 1980, Muram et al found that evidence of hormonal dependence includes the increased frequency of leiomyoma after menarche and growth of leiomyoma during pregnancy[12-18].

SITES OF OCCURRENCE

1. Uterine corpus (commonest)
2. Cervix
3. Broad ligament
4. Along other pelvis ligament.
5. Parasitic
6. Ovary (Tsalacopouls H et al 1981)

Within the uterus tumors can be

1. Intramural-75%
2. Subserosal-10%
3. Submucosal-15% (Shaw et al)

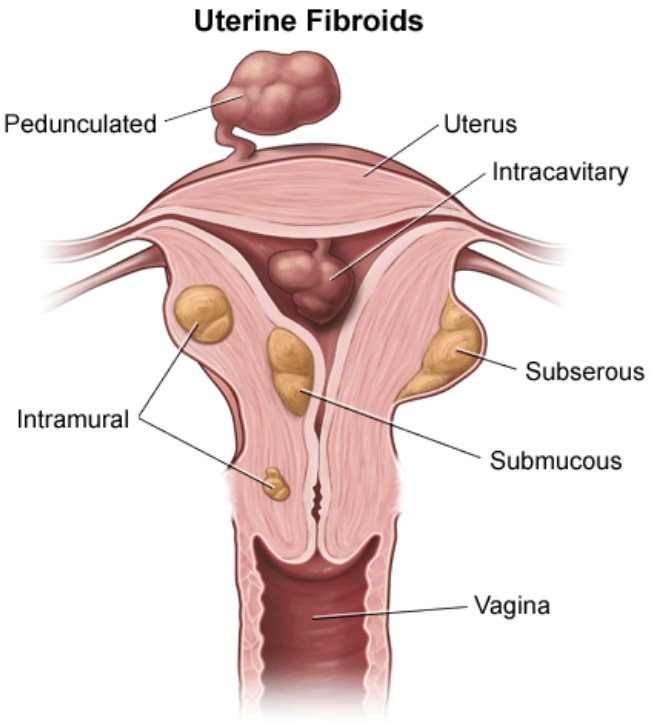


Figure 21- Sites of fibroid

CLINICAL FEATURES (Telinde et al)

Abnormal menstruation is the common clinical picture[12].

One third (30%) of patient present with menstrual complaints.

This can be in the form of

1. Menorrhagia
2. Metrorrhagia
3. Polymenorrhoea
4. Dysmenorrhoea or combination of these

PRESSURE SYMPTOMS

This is the second most common clinical presentation. These symptoms are mainly due to the pressure effect of the leiomyoma on the surrounding structures. They may present in the form of difficulty and frequency in micturition, constipation, low back ache or pain and discomfort in the lower abdomen. Importantly, 30% of the patients come to us with complaints of pain[12-18].

MASS ABDOMEN

Few of the patients may present with the complaints of only mass abdomen[12-18].

REPRODUCTIVE FAILURE

It must be remembered that sometimes fibroids remains the cause of infertility or recurrent pregnancy loss [12-18]. But it is rare (5%)

Symptoms produced by leiomyoma are dependent on the location of the tumor within uterus

Location	Menstrual	Pain	Integrity	Bulk
Intracavitary	+	+	+	-
Submucosal	+	+	+	-
Intramural	+	+	+	-
Subserosal	-	+	-	+
Pedunculated	-	+	-	+

LEIOMYOMA -VARIANTS [12-18]

- Ceullar leiomyoma
- Haemorrhagic cellular leiomyoma
- Epithelioid leiomyoma
- Symplastic leiomyoma
- Myxoid leiomyoma
- Leiomyoma with heterologous element

LEIOMYOMA - UNUSUAL GROWTH PATTERN

- Diffuse leiomyomatosis
- Intravascular leiomyoma
- Benign leiomyoma
- Differentiated peritoneal leiomyoma

GROSS

Leiomyoma are solid and white most frequently. They have a whorled appearance on cut surface. Ackerman et al in 1990 found that 84% of leiomyoma were multicentric[12-18].

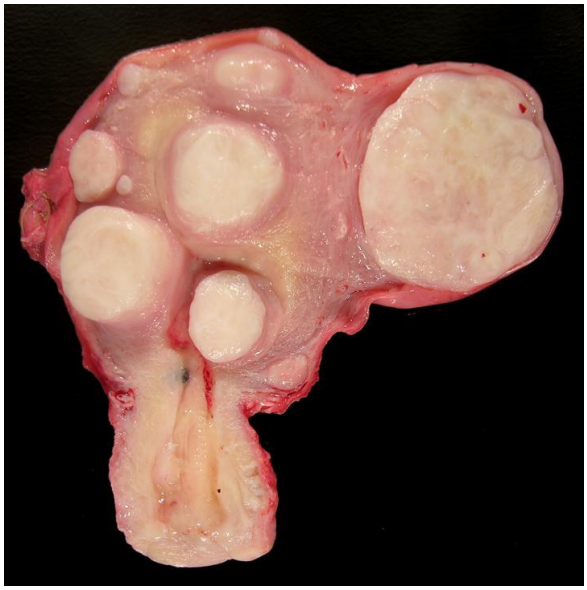


Figure 22 – Gross of leiomyoma

MICROSCOPIC FEATURES

Leiomyoma is composed of interlacing fasicles and bundles of smooth muscle cells. The smooth muscle cells are markedly elongated having eosinophilic cytoplasm and elongated cigar shaped muscle. In an uncomplicated cases, it's nuclei are uniform and mitotic figures absent or sparse. Abdundant reticulin is present[12-18].

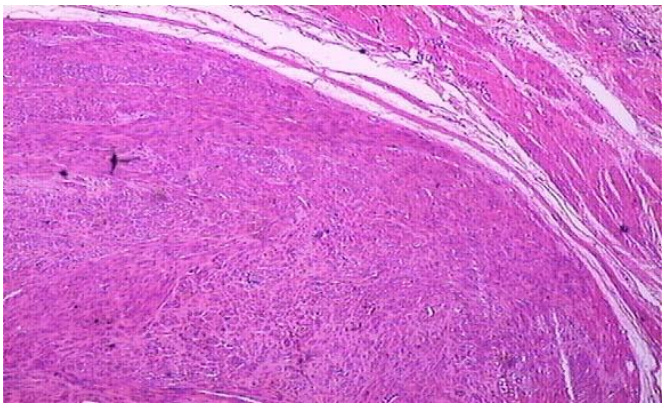


Figure 23 – Microscopy of leiomyoma

DEGENERATIVE CHANGES

Punnonem in 1965 and Arjoon in 1970 found that most forms of degenerations occurs as a result of replacement of muscle fibres by hyaline, collagen, blood, calcium, mucopolysaccharide or combination of these in their studies.

In 1964, Guptha and Hunter found that cells are admixed with smooth muscle cells in leiomyoma. In 1972, Christopher et al reported cellular leiomyoma to be more common in older women with uterine atrophy. In the same study, they also reported on symplastic leiomyoma. These are nothing but benign smooth muscle tumor of uterus which contain large bizarre cells with large nucleus. Mitotic count is less than 2/10 HPF. In 1972, Willamson E.O and Christopherson reported that leiomyoma arising near serosa especially with pedicle may take up the blood supply from the nearby organs and get detached themselves. These are called as parasitic leiomyoma[12-18].

In 1977, Gasser and young reported neurilemmoma like leiomyoma in their studies. Sometimes leiomyoma resembles neurilemmoma due to stromal hyalinization. They usually demonstrate smooth muscle differentiation ultra structurally. In 1980, Mazur and Kraus reported tubular differentiation in otherwise characteristic leiomyoma. In 1991, Hu.John Surti et al found that cytogenetic alterations are common in uterine leiomyoma. The most common are rearrangements of 6p del7qt12 and t12 (12:14)[12-18].

Mason tc et al. in 2002 found red degeneration of leiomyoma masquerating as retained products of conception. The incidence of leiomyoma in pregnancy is approximately 1%. Their presence has been linked to spontaneous abortion, fetopelvic disproportion, malposition of fetus, premature labor, soft tissue dystocia, uterine inertia, post partum haemorrhage and retention of placenta.

Discovering calcified uterine myomas is not frequent. Three cases of uterine myoma are reported as cause of pelvic calcification and to establish differential diagnosis with bladder stones[12-19]. Diagnosis is made by radiological studies in postmenopausal patients (Hermida Perez et al 2003)

UTERINE PROLAPSE AND LEIOMYOMA

In 2004, Mittak Y et al study investigated the frequency and implications of incidental findings in uteri which are removed for clinical picture of prolapse. They found a high frequency of incidental findings[12].

LEIOMYOMA OF UTERUS AND ASSOCIATED CONDITIONS

LEIOMYOMA OF UTERUS CORRELATION WITH CYCLICAL CHANGES IN ENDOMETRIUM

The endometrium undergoes primarily histophysiological and age-related changes in the presence of leiomyoma. (Zheleznov BI et al 1990).Endometrial structures were normal in 54% of 178 myoma patient and phases of incomplete secretion were recorded in 14.6% (Zentral BI et al gynakol 1982, Landecho wshij JD et al 1982).

LEIOMYOMA AND ENDOMETRIAL THICKNESS

L.Deligdish et al study of endometrium with myoma, atrophic endometrium were the most constant morphological changes in the presence of uterine mainly submucous myoma (83%). Atrophy may result not only from mechanical pressure but also from postmenpausal hormonal insufficiency [12]. The myometrial tumor is large and the overlying endometrium may be thinned out.

LEIOMYOMA AND ENDOMETRIAL HYPERPLASIA

According to Block et al (1961) the association between uterine myoma and endometrial hyperplasia varied between 6% and 80%. Goranjon, Ganotti et al (1961) found high oestrogen levels in woman with uterine fibroid and believed that the endometrium played a vital role in the synthesis of estrogens.

Hyperplasia is the most common change seen in the endometrium associated with fibroid uterus. (Acta Obs. Gynae. 1963).Teleman S et al (2003) studied 390 specimens of hysterectomy. 316 cases presented with different degrees of endometrial hyperplasia associated with leiomyoma. Leiomyoma and endometrial hyperplasia development is a hormonal context. The most frequent type is simple hyperplasia suggesting a rare progression to the highest grades[12-18].

The authors analysed 600 patients with uterine leiomyoma from hysterectomy which were performed for the conditions when leiomyoma were also studied for control purpose. Major conditions are endometrial hyperplasia. (Szajnbok et al 1990)

Biopsy specimens of the endometrium are obtained from the 154 cases diagnosed. It showed functional uterine bleeding has the higher incidence followed by myoma of the uterus.

Endometrium in association with myoma shows a little or no departure from the normal and the histological sequence of cyclic changes may occur just as it does in the ovulatory cycle of non-myomatous patient. On the other hand, in considerable proportion of case he finds an association of non ovulatory type of cycle with myoma with frequently a hyperplasia of the endometrium of more or less marked degree.Endometrial hyperplasia was recordable primary from patient with menopausal ovarian dysfunction in patient with uterine myoma (Lond et al, 1982).

In 103 out of 786 patients with hyperplasia, myomatous changes were noted. This finding correlated with hyperestrogenism, which is usually present in both disorders (Todorovic N et al, 2002).

ADENOMYOSIS

Adenomyosis of the uterus is a condition which is characterized by a benign invasion of the endometrium into the uterine musculature and is associated with diffuse overgrowth of uterus[20-28].Adenomyosis is found in 25 to 40 % of all hysterectomy specimens by Bird and associates. (Bird C et al 1972).

In adenomyosis, the uterus may be slightly or markedly enlarged though the increase in size never reaches large that is seen so often with myoma[20-28].

However, it must be remembered that adenomyosis and myoma often co exist, the myoma being responsible for the frequently large size of the uterus in such cases[33].

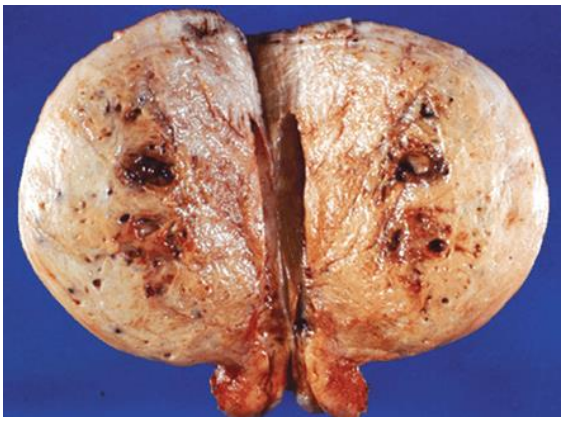


Figure 24 – Gross of adenomyosis

Adenomyosis results grossly in an enlarged and bulky uterus because of the myometrial hypertrophy that regularly accompanies it.On cut section, the diagnosis may be suspected by the presence of depressed small cystic lesions in obvious but ill defined bulging zone of muscle hypertrophy[20-28]. The cause of endometrial and muscle growth is the estrogenic hormone secreted by the ovary lending the support to the belief that adenomyosis will be found to be considered as an endocrine dysfunction of the ovary [28,40]

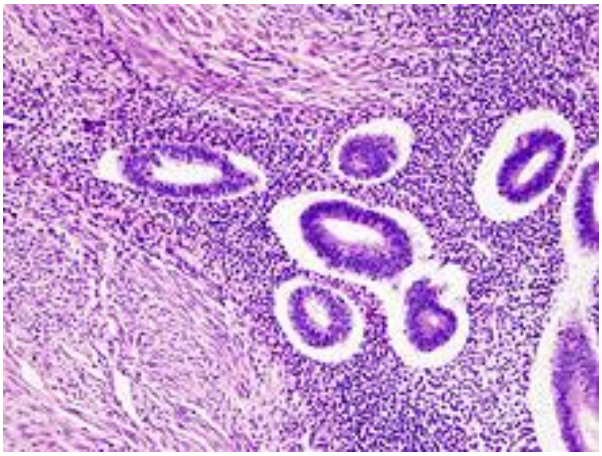


Figure 25 – Microscopy of adenomyosis

LEIOMYOMA AND ADENOMYOSIS

Uterine fibroma is associated in 62% of cases in Ben Aissia N et al study of analysis of 35 cases of adenomyosis, (Tunis med.2001). Adenomyosis is more frequently associated with leiomyoma but essential adenomyosis was diagnosed most constantly when uterine enlargement was noted during menstrual period. (Thomas TS Jr et al 1989).

Adenomyosis was noted in 16% of 2, 616 consecutive hysterctomy specimens which were examined during a period of 7 year. Multiparous women between the ages 30 and 50 years were most commonly affected[37]. Abnormal uterine bleeding was the common symptom. Myohyperplasia, leiomyoma were usually associated lesion. It is seen equally in women of Africa, India and mixed races in the West Indian population (Raju GC et al 1988)

LEIOMYOMA AND ENDOMETRIAL CARCINOMA

There are a few reported cases of endometrial carcinoma in association with leiomyoma. The percentage varies 0.2 to 16.2% (Dupantier N et al 2003, Tatamizawa S et al 1999, Studzinki Z et al 2000, Cabrerce J et al 1994, Studzinski et al 1998). According to Zhonghua L et al 1990, there is no association of endometrial carcinoma and leiomyoma[27].

Materials & Methods

MATERIALS AND METHODS

AIM OF STUDY

To study the changes of endometrium in association with myometrial lesions of hysterectomy specimens with respect to various clinical and morphological features.

OBJECTIVES OF THE STUDY

To analyse the histopathological changes of endometrium in association with myometrial lesions of hysterectomy specimens in our Institution with respect to LMP and age.

To assess the age distribution of the myometrial lesions in patients subjected to hysterectomy.

To assess the endometrial changes in relation with the types and sites of myometrial lesions in hysterectomy specimens.

Type of study : Analytical Study

Place of study : Department of Pathology, TSRMMCH & RC, Trichy.

Sample size : 250 cases

Study design : Descriptive (Prospective and Retrospective) study

INCLUSION CRITERIA

Patients undergoing hysterectomy for myometrial lesions presenting with clinical symptoms.

EXCLUSION CRITERIA

- Specimens of endometrial curettage and aspiration.
- Patients for whom hysterectomy is performed for non-myometrial lesions.

DATA ANALYSIS : By SPSS(Statistical Package for the Social Sciences) Software

SAMPLE SIZE AND SAMPLING:

This was a prospective and retrospective study performed on hysterectomy specimens received at the Department of Pathology, Chennai Medical College Hospital and Research Centre for a period of one and half years from November 2016 to June 2018 after getting ethical clearance. A total of 250 cases in all age group were included in the study. The endometrial patterns were analyzed in hysterectomy specimens with myometrial lesions.

BRIEF METHODOLGY FOR STUDY DESIGN

The endometrium will be studied for the patients who underwent hysterectomy for clinical symptoms of myometrial lesions. 10% buffered formalin will be used for fixation of specimens.

A total of 250 hysterectomy specimens with myometrial lesions are taken. A detailed gross examination was performed with respect to location and size of

leiomyoma, and status of endometrium and endometrial polyp if any was noted.Tissue bits from representative areas of the leiomyoma and endometrium were taken for histopathological examination, processed and paraffin blocks were made. Sections were cut at 5-micron thickness and stained with hematoxylin and eosin. Microscopic sections were studied and following histologic features were recorded:

Endometrial parameters - endometrium, phase, appearance of glands and stromal changes.

Myometrial parameters- presence or absence of adenomyosis, type or variant of leiomyoma.

HEMATOXYLIN AND EOSIN STAIN PROCEDURE

1. Deparafffinise the tissue sections in xylene for 5-10 mins.
2. Subject the tissue section to water through reducing grades of alcohol.(100% - 50%)
3. Keep it in hematoxylin for15 to 20 mins.
4. Rinse in tap water.
5. Differentiate with 1%acid alcohol.
6. For bluing – place in tap water for about 10 mins.
7. Counterstain by eosin 1-2mins.
8. Rinse in water.
9. Dehydration followed by clearing and mounting it.

Observation & Results

OBSERVATION AND RESULTS

Table 1 - AGE DESCRIPTION OF THE PATIENTS

Minimum	Maximum	Mean	Std. Deviation
32	67	44.61	5.96

Comments:

The mean age of the patients was 44.61 ± 5.96 years.

The minimum and maximum age of the patients was 32 and 67 years respectively.

Table 2 - AGE WISE DISTRIBUTION OF PATIENTS

Age in years	No. of cases	Percent
30-39	40	16.0
40-49	170	68.0
50-59	33	13.2
60-69	7	2.8
TOTAL	**250**	**100**

Comments:

Out of 250 patients, 68% (170) patients were from the age group 40 to 49 years. It was followed by patients from 30 - 39 years, 16% (40) and 50 - 59 years, 13.2% (33). The least number of patients were from the age group 60 - 69 years, 2.8% (7).

Graph 1 - Distribution of patients according to age group

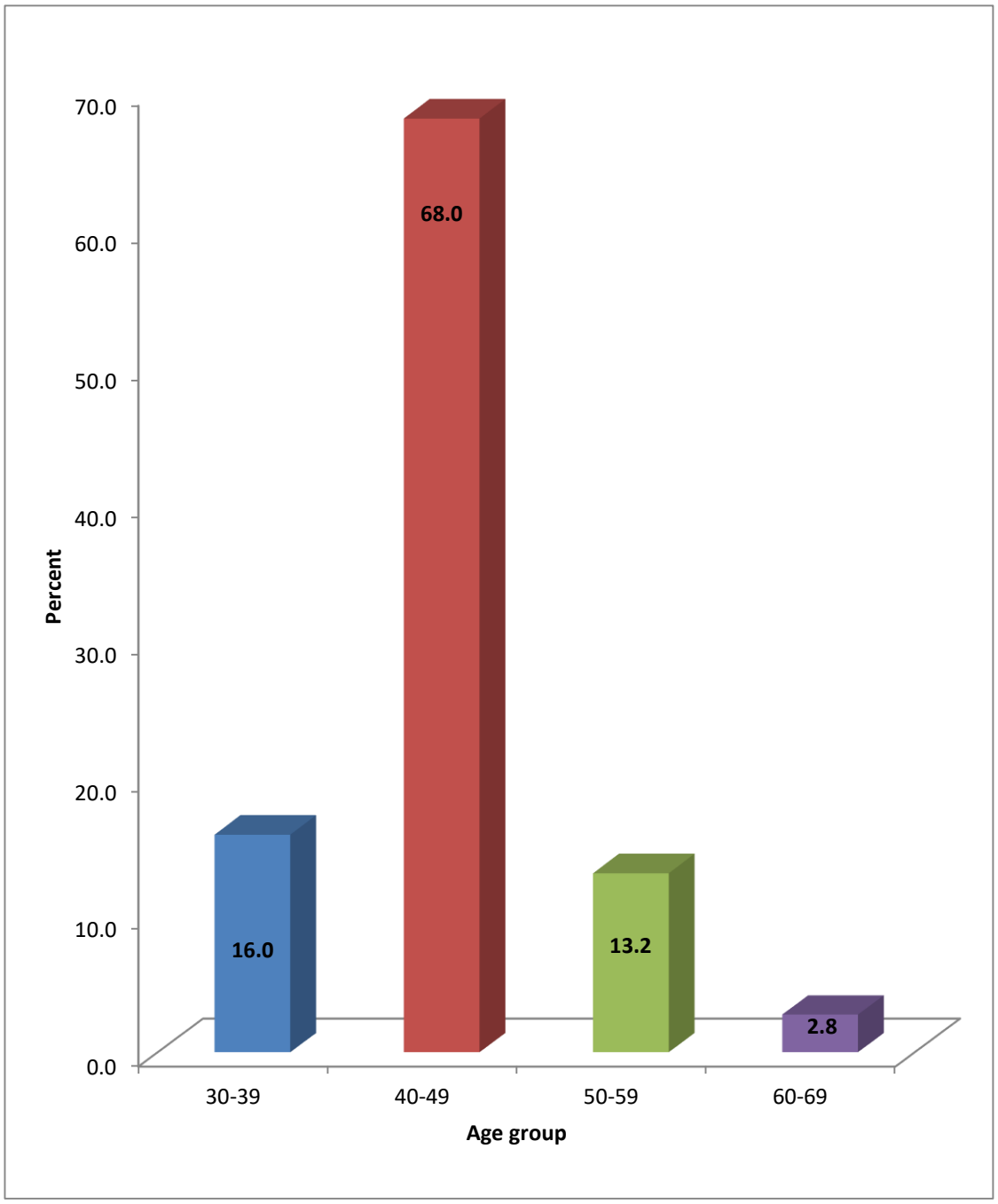


Table 3 – Distribution of endometrial changes according to age group

ENDOMETRIAL CHANGES	AGE RANGE IN YEARS							
	30 - 39		40 - 49		50 - 59		60 – 69	
	F	P	F	P	F	P	F	P
PP	10	25.0	39	22.9	3	9.1		
ES	16	40.0	51	30.0	8	24.2		
LS	5	12.5	33	19.4	2	6.1		
DPP	3	7.5	22	12.9	2	6.1		
SH	6	15.0	18	10.6	4	12.1		
CH			1	.6				
Atrophic			5	2.9	13	39.4	6	85.7
EIN			1	.6				
EC					1	3.0		
Others							1	14.3
TOTAL	**40**	**100.0**	**170**	**100.0**	**33**	**100.0**	**7**	**100.0**

Graph 2 - Endometrial changes according to the age group

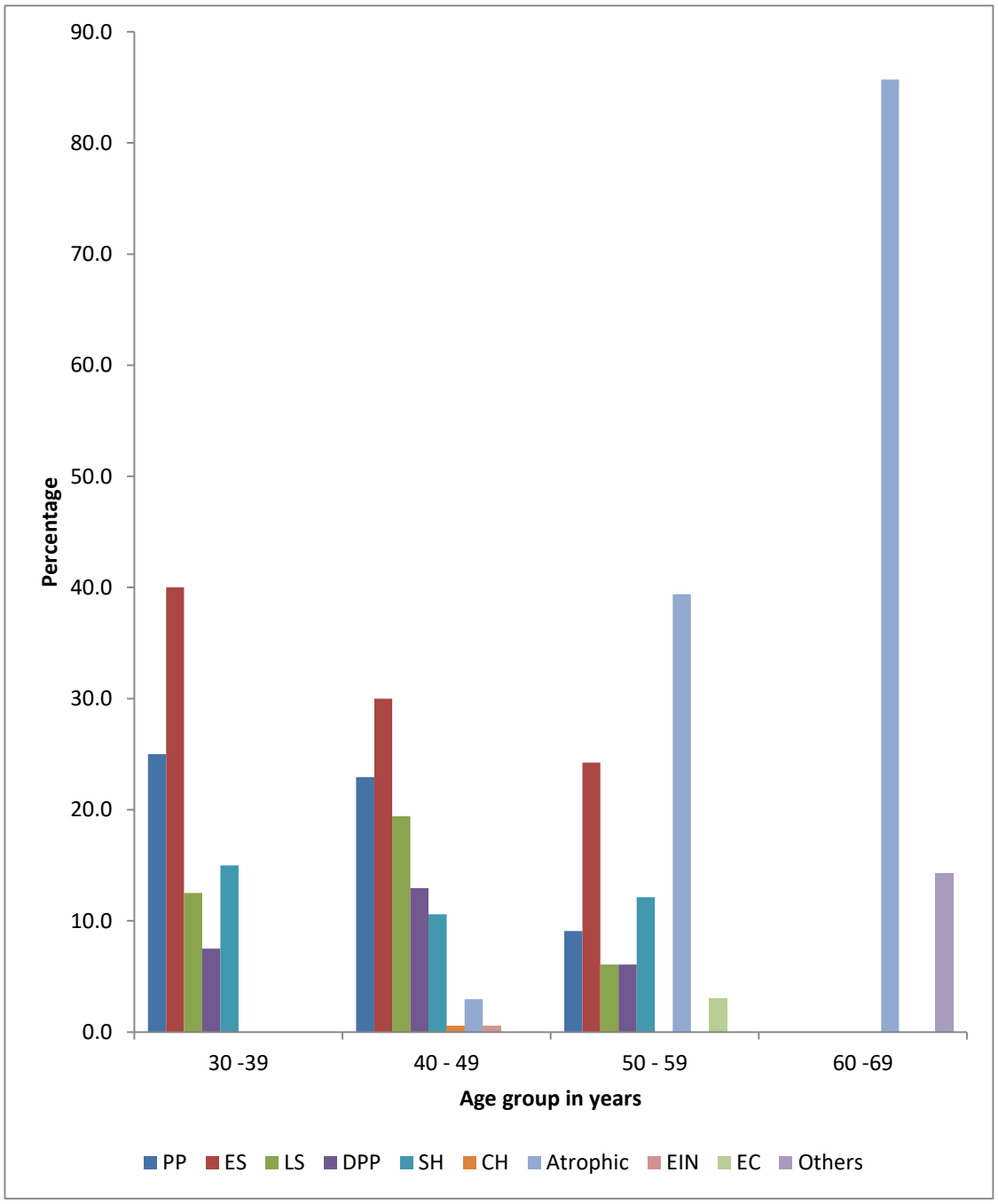


Table 4 - DISTRIBUTION OF LEIOMYOMA BASED ON LOCATION IN UTERUS

S.No.	Location	Frequency	Percent
1	Intra mural	132	52.8
2	Sub mucous	36	14.4
3	Sub serous	23	9.2
4	Intra mural and Sub mucous	25	10.0
5	Intramural and Subserous	20	8.0
6	Sub mucous and Sub serous	6	2.4
7	Intramural, Submucous and Subserous	8	3.2
TOTAL		**250**	**100.0**

Comments:

Most number of leiomyomas were located intramurally 52.8% (132). It was followed by submucous [14.4% (36)] and intramural and submucous combination [10% (25)] location. The number of cases with subserous and combination of intramucous and subserous was 9.2% (23) and 8% (20) respectively. Least number of cases were located in submucous and subserous combination [2.4% (6)] and intramural, subserous, submucous combination [3, 2% (8)]

Graph 3 - Distribution of Leiomyoma according to site

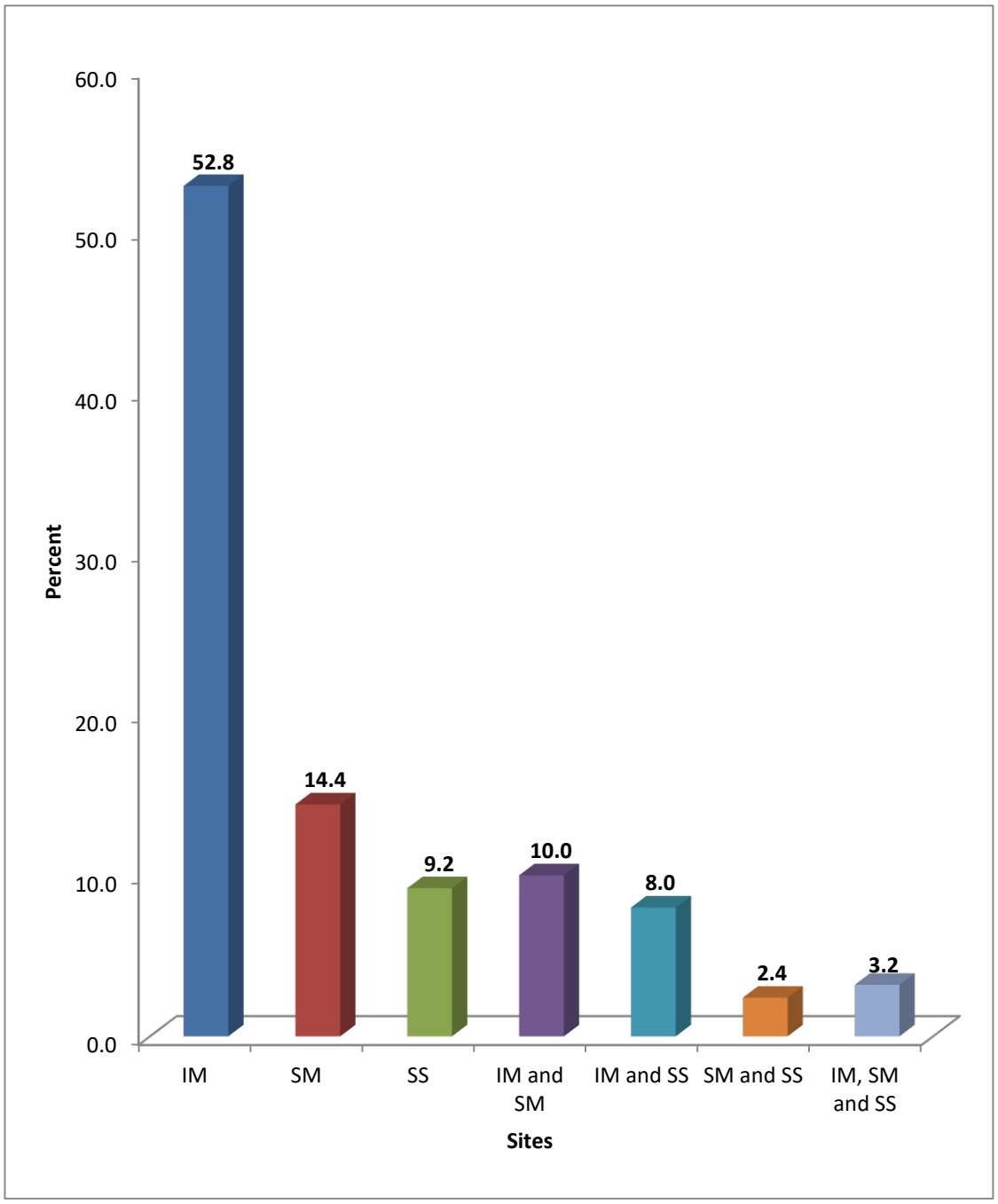


Table 5 - DISTRIBUTION OF LEIOMYOMA OF UTERUS BASED ON NUMBER

Number	Frequency	Percent
Single	173	69.2
Multiple	77	30.8
TOTAL	**250**	**100.0**

Comments:

Majority of the cases reported were single [69.2% (173)]. Totally 77 cases (30.8%) reported were multiple in number.

Graph 4 - Distribution of Leiomyoma according to number

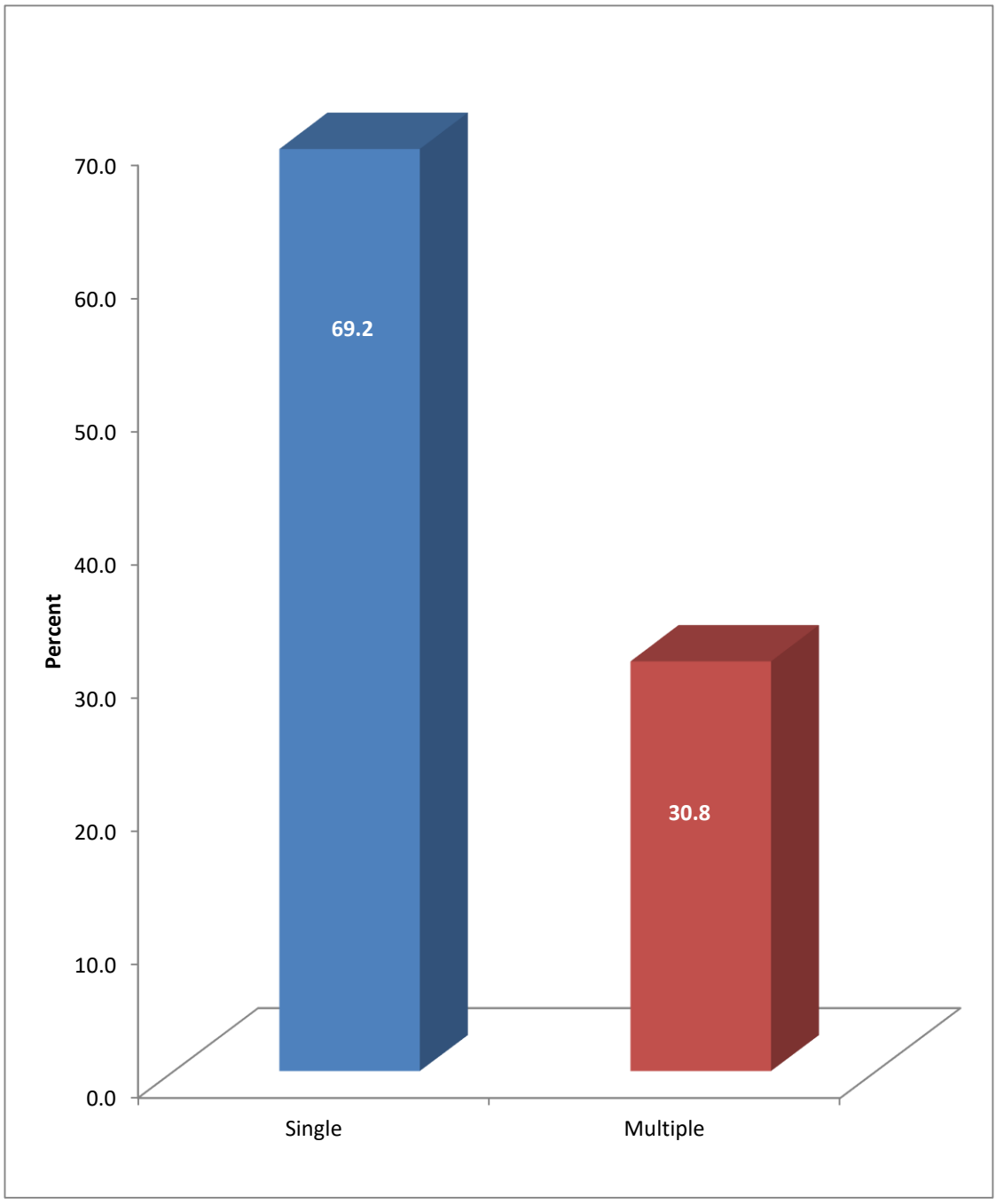


Table 6 - DISTRIBUTION OF ENDOMETRIAL CHANGES IN LEIOMYOMA

S.No.	Endometrial Change	Frequency	Percent
1	Proliferative Phase	52	20.8
2	Early Secretory Phase	75	30
3	Late Secretory Phase	40	16
4	Disordered proliferative phase	27	10.8
5	Simple Hyperplasia	28	11.2
6	Complex Hyperplasia	1	0.4
7	Atrophic Endometrium	24	9.6
8	Endometrial intraepithelial neoplasia	1	0.4
9	Endometrial carcinoma	1	0.4
10	Others	1	0.4
	TOTAL	**250**	**100.0**

Comments:

Thirty percent (75) of the cases reported was associated with early secretoryphase. The percent of cases associated with proliferative phase and late secretory phases were 20.8% (52) and 16% (40) respectively. The percent of cases associated with simple hyperplasia, disordered proliferative phase and atrophic endometrium were 11.2% (28), 10.8% (27) and 9.6% (24) respectively. There was one (0.4%, totally 2%) case of each - complex hyperplasia, Endometrial intraepithelial invasion, endometrial carcinoma and other.

Graph 5 - Distribution of endometrial changes in leiomyoma

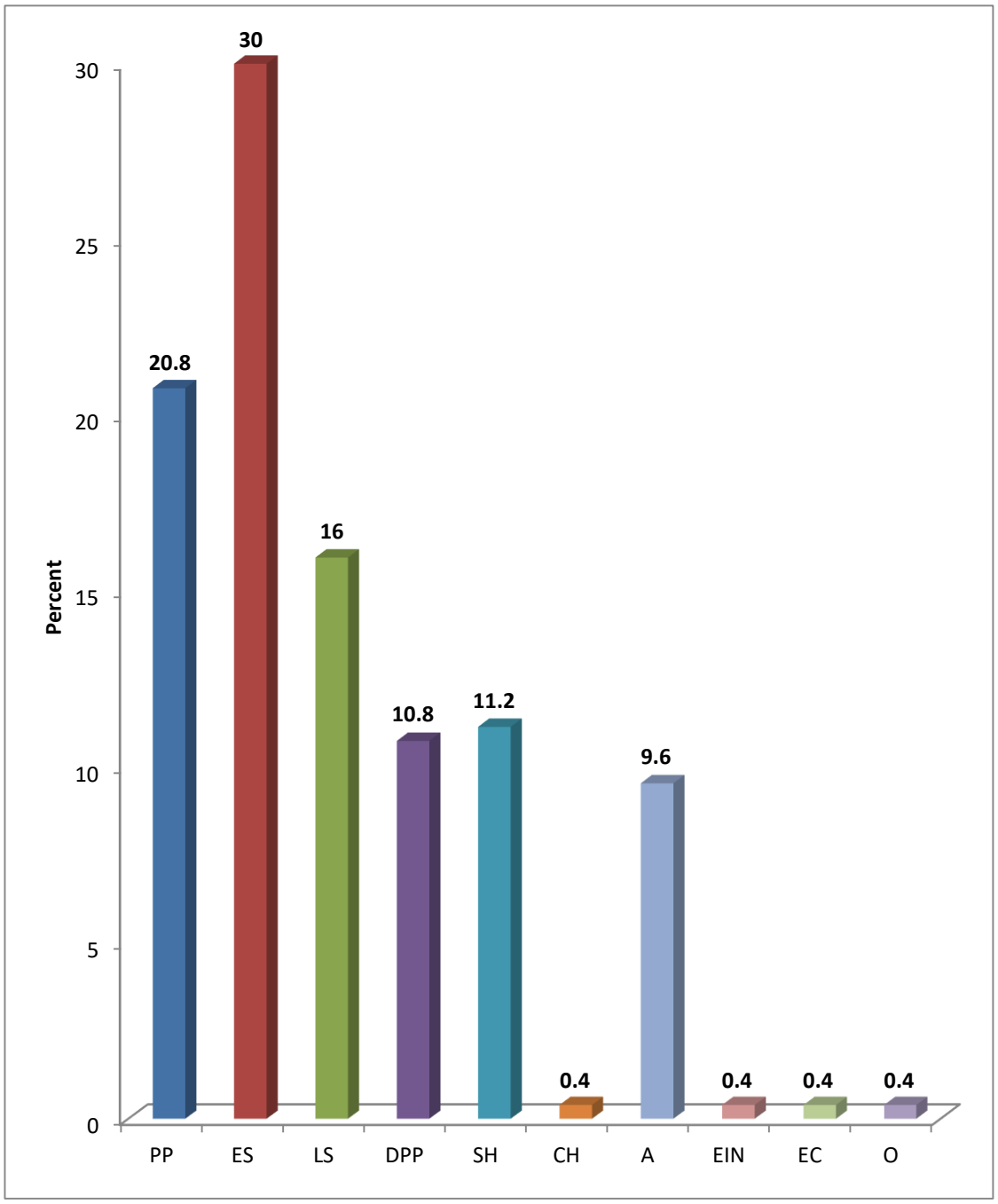


Table 7 – Distribution of endometrial changes according to the site of leiomyoma

ENDOMETRIAL CHANGES	LOCATION OF LEIOMYOMA													
	IM		SM		SS		IM + SM		IM + SS		SM + SS		IM + SM + SS	
	F	P	F	P	F	P	F	P	F	P	F	P	F	P
PP	23	17.4	10	27.8	3	13.0	7	28.0	4	20.0	4	66.7	1	12.5
ES	43	32.6	9	25.0	9	39.1	3	12.0	7	35.0			4	50.0
LS	23	17.4	7	19.4	3	13.0	3	12.0	2	10.0	2	33.3		
DPP	13	9.8	1	2.8	2	8.7	6	24.0	3	15.0			2	25.0
SH	15	11.4	4	11.1	1	4.3	5	20.0	2	10.0			1	12.5
CH	1	.8												
Atrophic	12	9.1	5	13.9	4	17.4	1	4.0	2	10.0				
EIN	1	.8												
EC	1	.8												
Others					1	4.3								
TOTAL	**132**	**100.0**	**36**	**100.0**	**23**	**100.0**	**25**	**100.0**	**20**	**100.0**	**6**	**100.0**	**8**	**100.0**

Graph 5 – Distribution of endometrial changes according to the site of leiomyoma

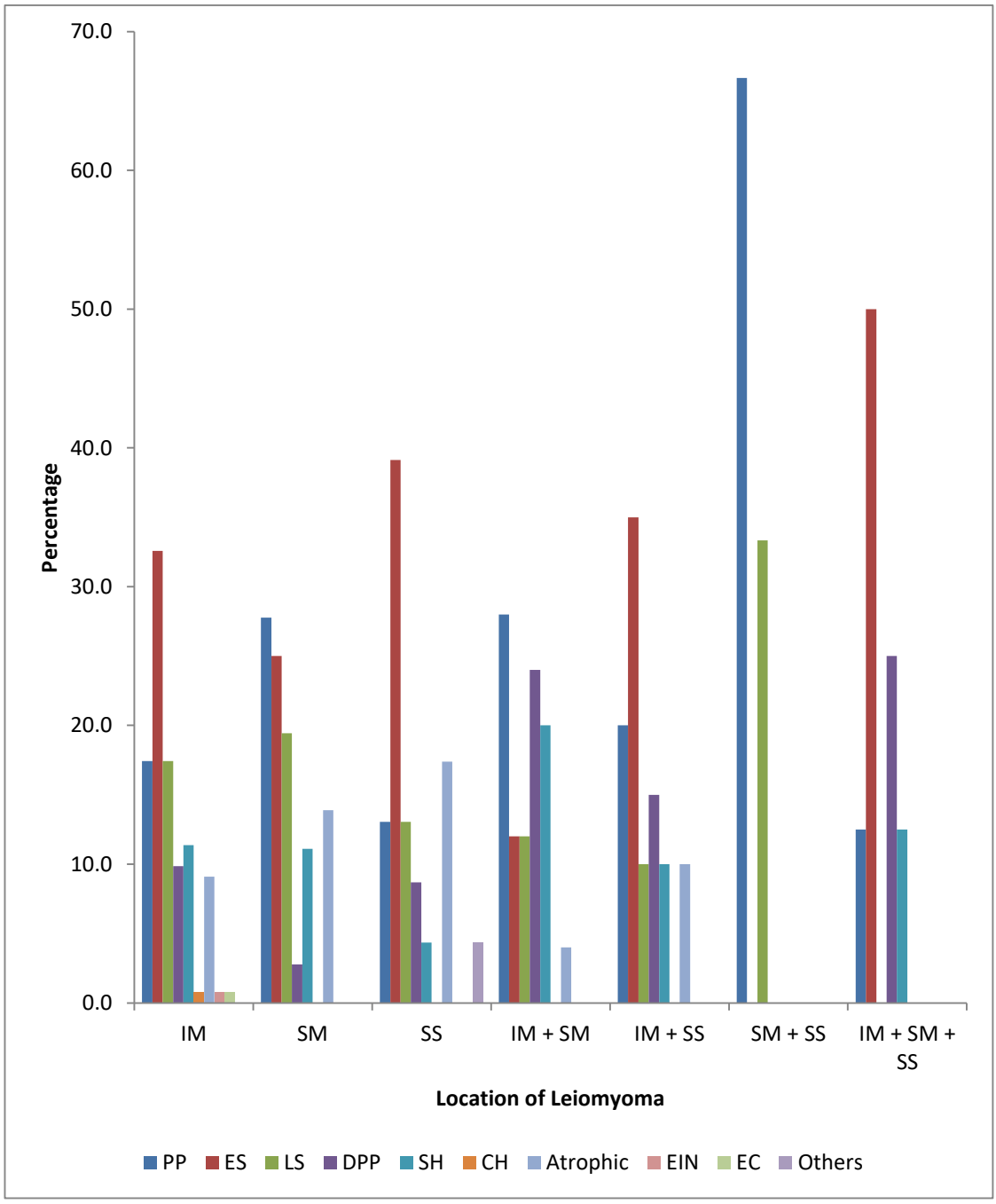


Table 8 - DISTRIBUTION OF LEIOMYOMA ACCORDING TO LMP

LMP in days	Frequency	Percent
< 7 days	7	2.8
7 to 15 days	55	22.0
16 to 30 days	97	38.8
> 30 days	59	23.6
Post menopausal	32	12.8
TOTAL	**250**	**100.0**

Comments:

Majority of the leiomyoma cases 38.8% (97) had LMP of 16 to 30 days. It was followed by LMP of greater than 30 days [23.6% (59)] and 7 to 15 days [22% (55)]. Only 2.8% (7) were associated with LMP of less than seven days. Leiomyomas associated with post menopause were 12.8% (32)

Graph 7 - Distribution of Leiomyoma according to LMP

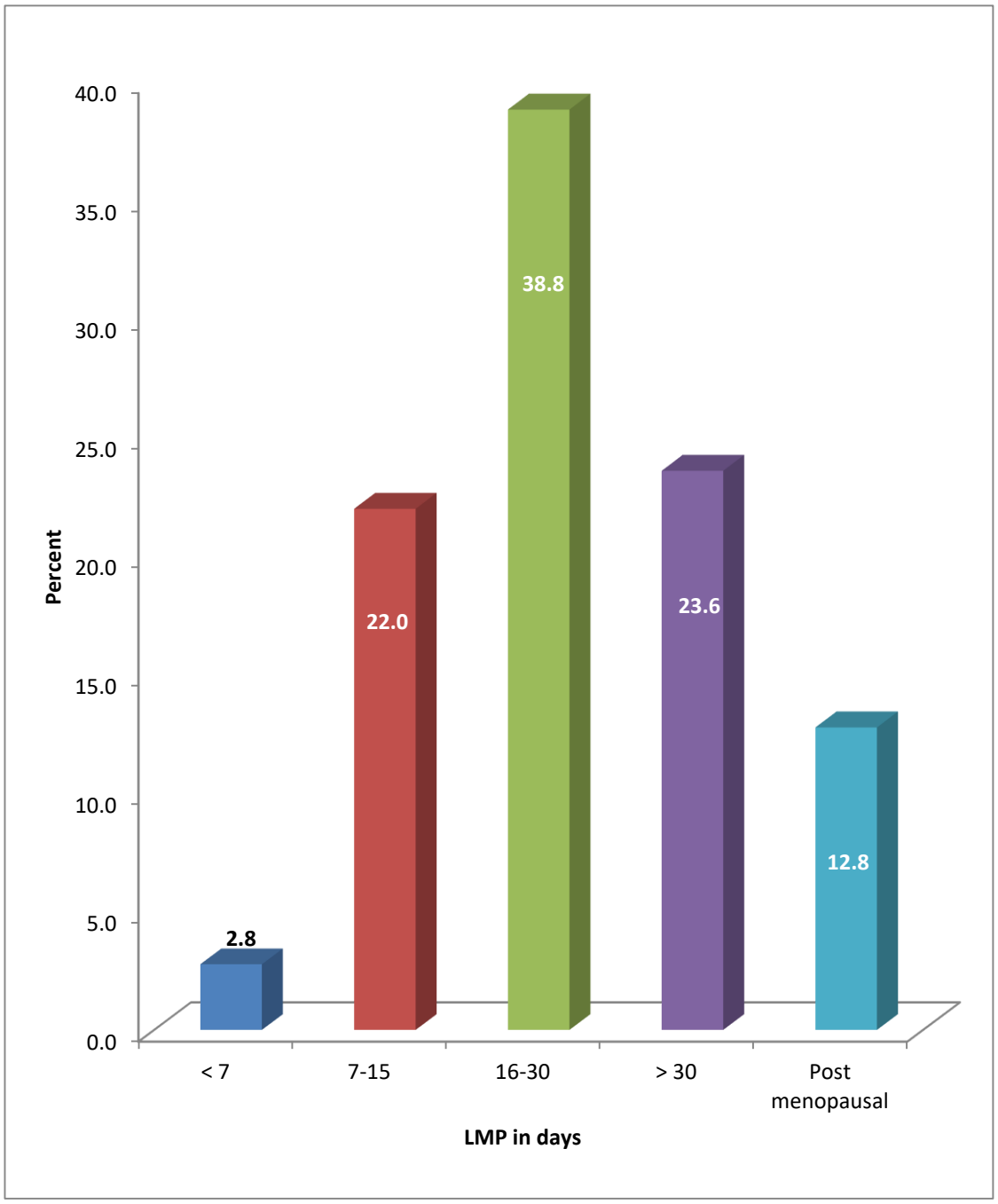


Table 9 – Distribution of endometrial changes according to LMP

ENDOMETRIAL CHANGES	LMP IN DAYS									
	<7		7 - 15		16 - 30		>30		Post menopausal	
	F	P	F	P	F	P	F	P	F	P
PP	2	28.6	20	36.4	17	17.5	7	11.9	6	18.8
ES	3	42.9	19	34.5	41	42.3	11	18.6	1	3.1
LS			2	3.6	12	12.4	26	44.1		
DPP	1	14.3	6	10.9	13	13.4	6	10.2	1	3.1
SH	1	14.3	7	12.7	10	10.3	8	13.6	2	6.3
CH							1	1.7		
Atrophic			1	1.8	3	3.1			20	62.5
EIN					1	1.0				
EC					97	100.0			1	3.1
Others									1	3.1
TOTAL	**7**	**100.0**	**55**	**100.0**	**97**	**100.0**	**59**	**100.0**	**32**	**100.0**

Graph 8 – Distribution of Endometrial changes according to the LMP

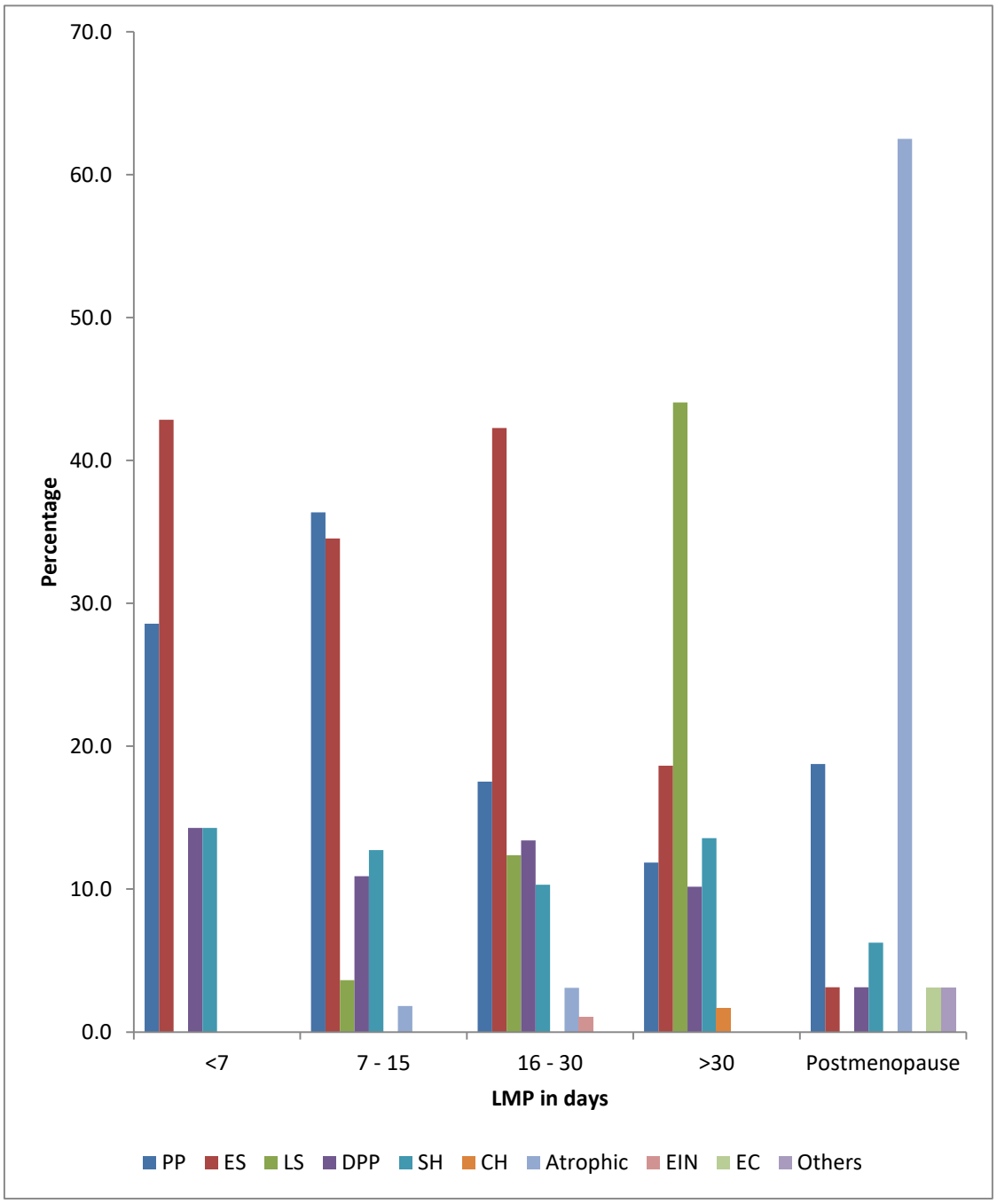


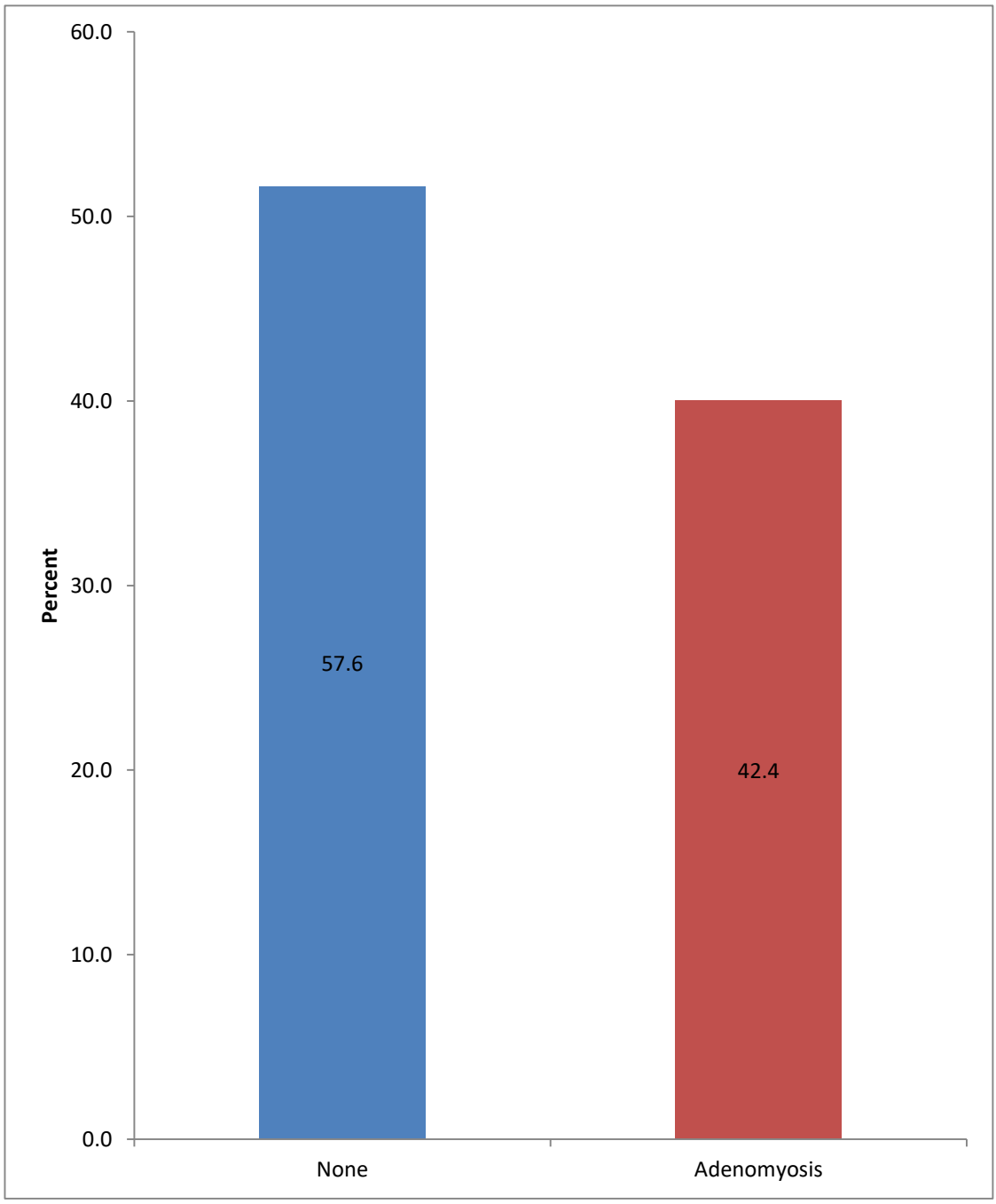
Table 10 - DISTRIBUTION OF ADENOMYOSIS IN LEIOMYOMA CASES

Lesion	Frequency	Percent
None	144	57.6
Adenomyosis	106	42.4
TOTAL	250	100.0

Comments:

Adenomyosis was present in 42.4% (106) of leiomyoma cases.

Graph 9- Distribution of adenomyosis in leiomyoma cases



COLOR PLATES

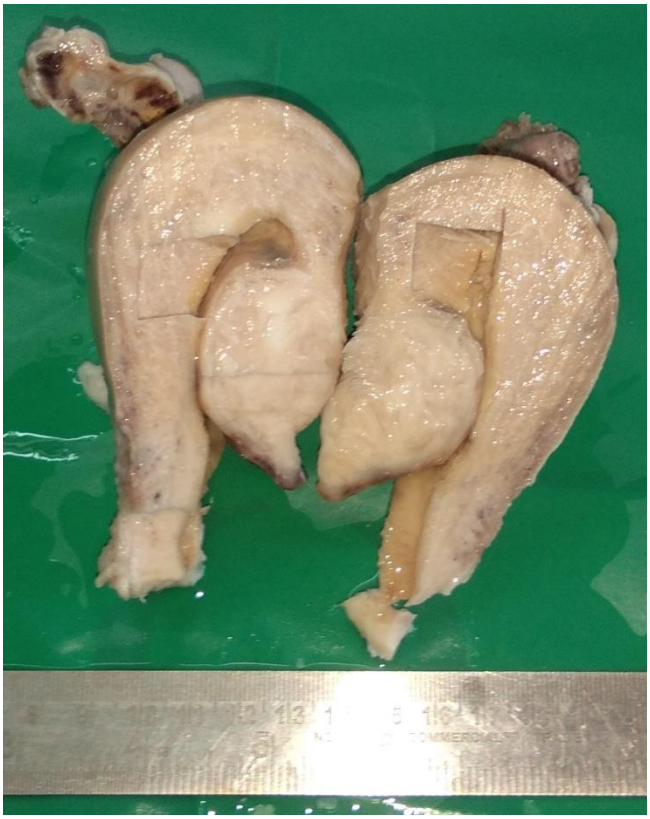


Figure i – H4483/16 – Submucous leiomyoma

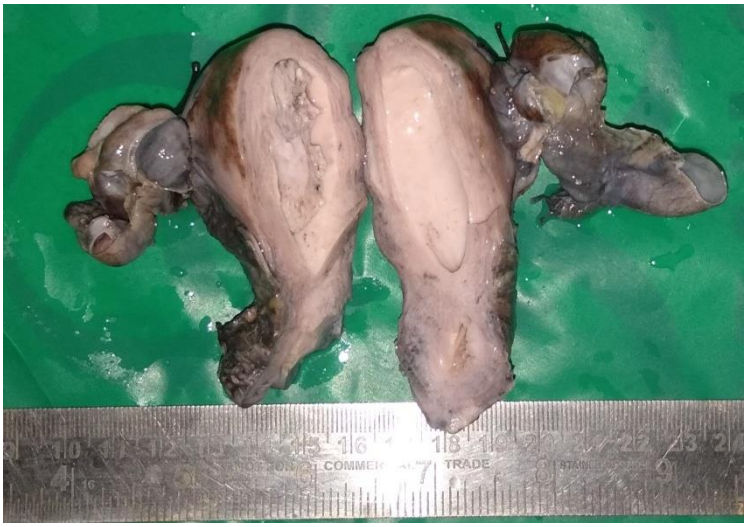


Figure ii – H4178/16 – Endometrial carcinoma

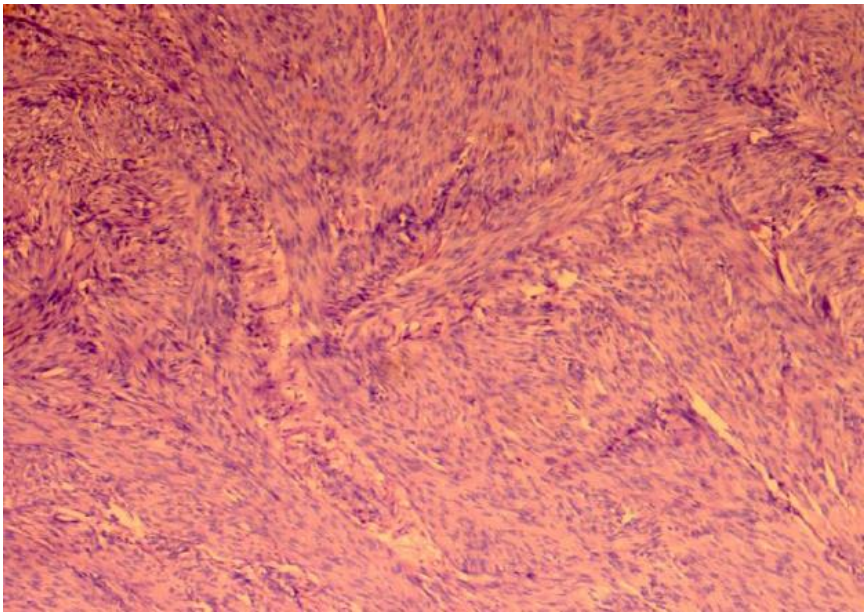


Figure iii -CLASSICAL LEIOMYOMA. (H&E4X) (H476/17)

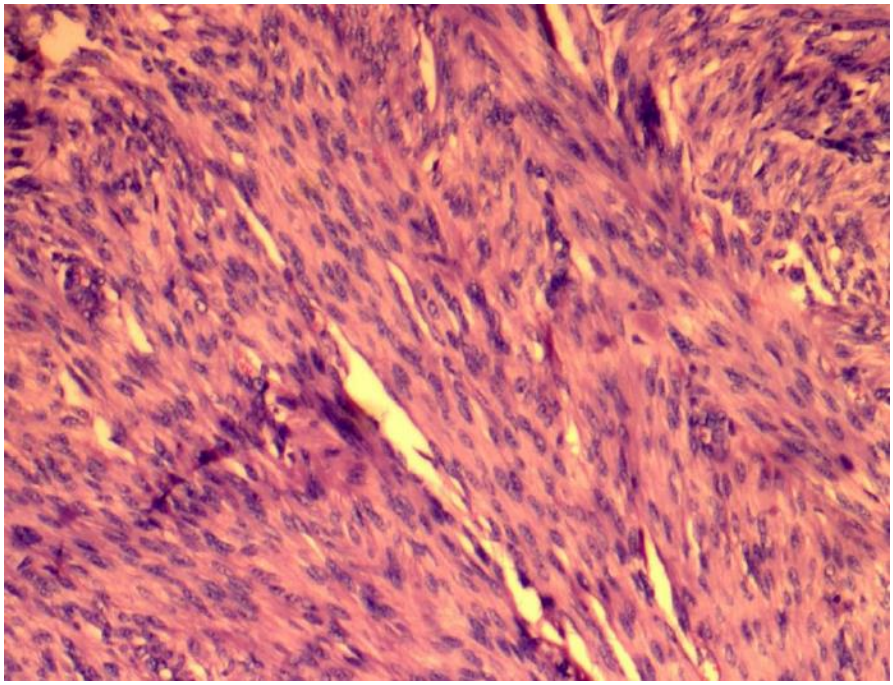


Figure iv - LEIOMYOMA SHOWING SPINDLE CELLS. (H&E10X) (H4296/17)

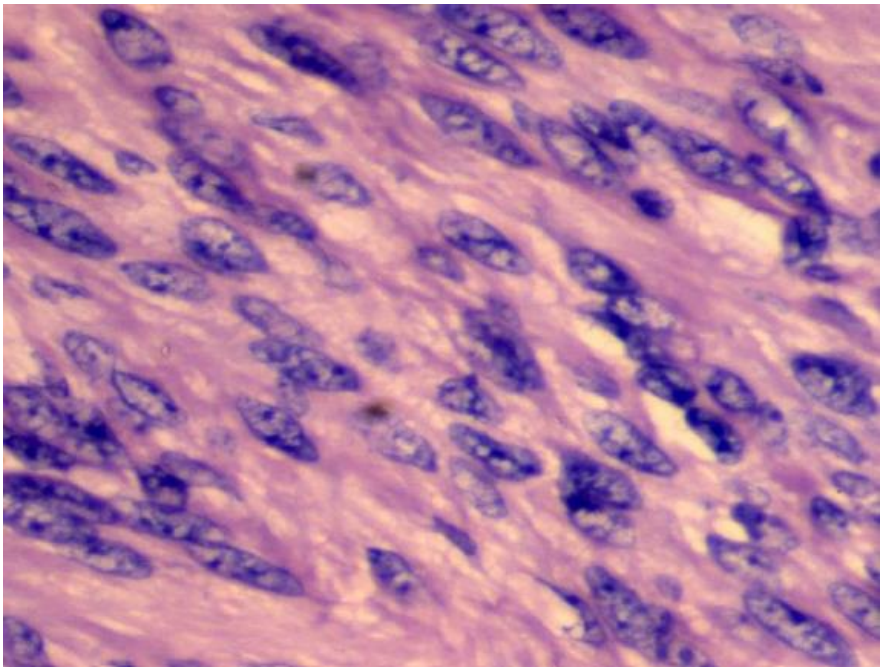


Figure v - LEIOMYOMA SHOWING NUCLEI WITH BLUNTED TIPS. (H&E 40X) (H4096/17)

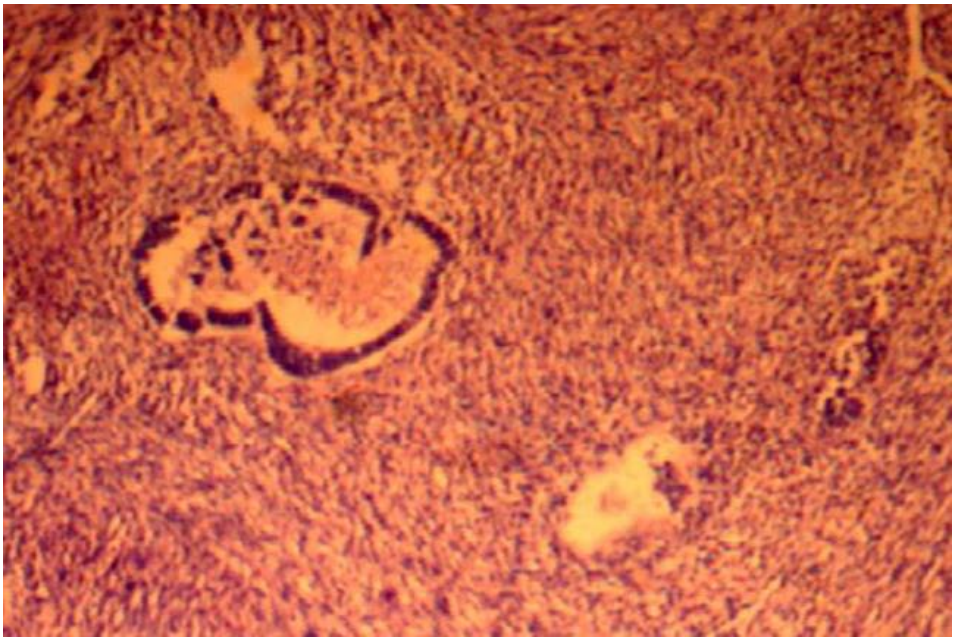


Figure vi- ADENOMYOSIS (H2807/16)

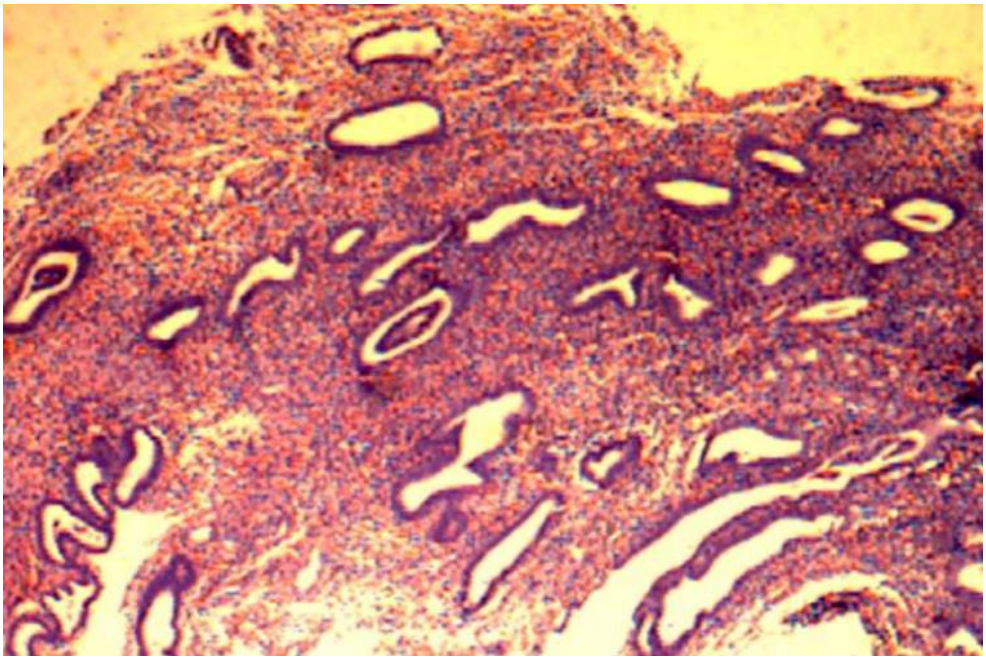


Figure vii - PROLIFERTIVE ENDOMETRIUM (H2732/16)

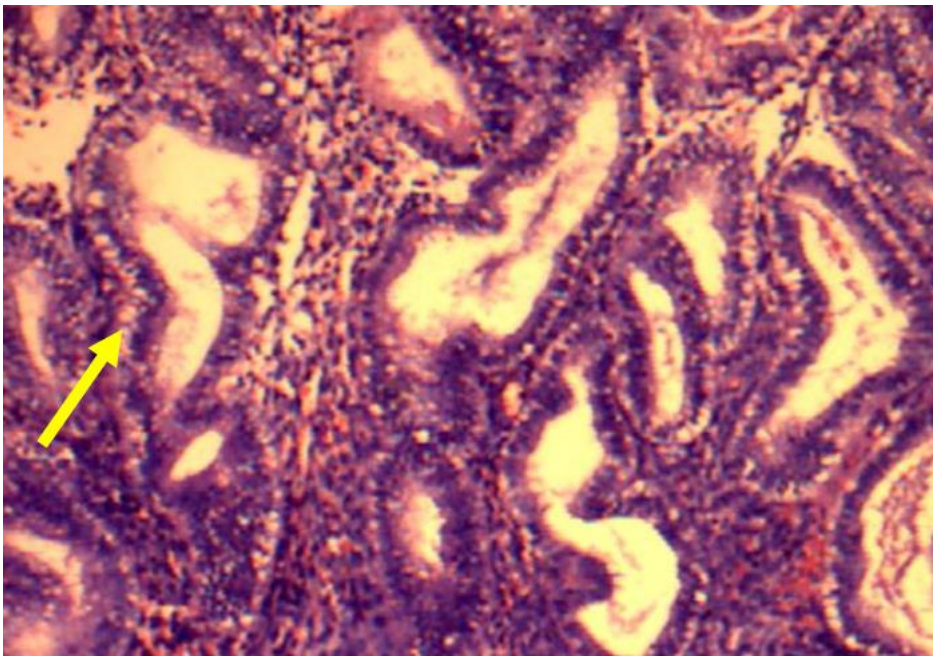


Figure viii - SECRETORY ENDOMETRIUM SHOWING SUBNUCLEAR VACUOLATION (H2484/16)

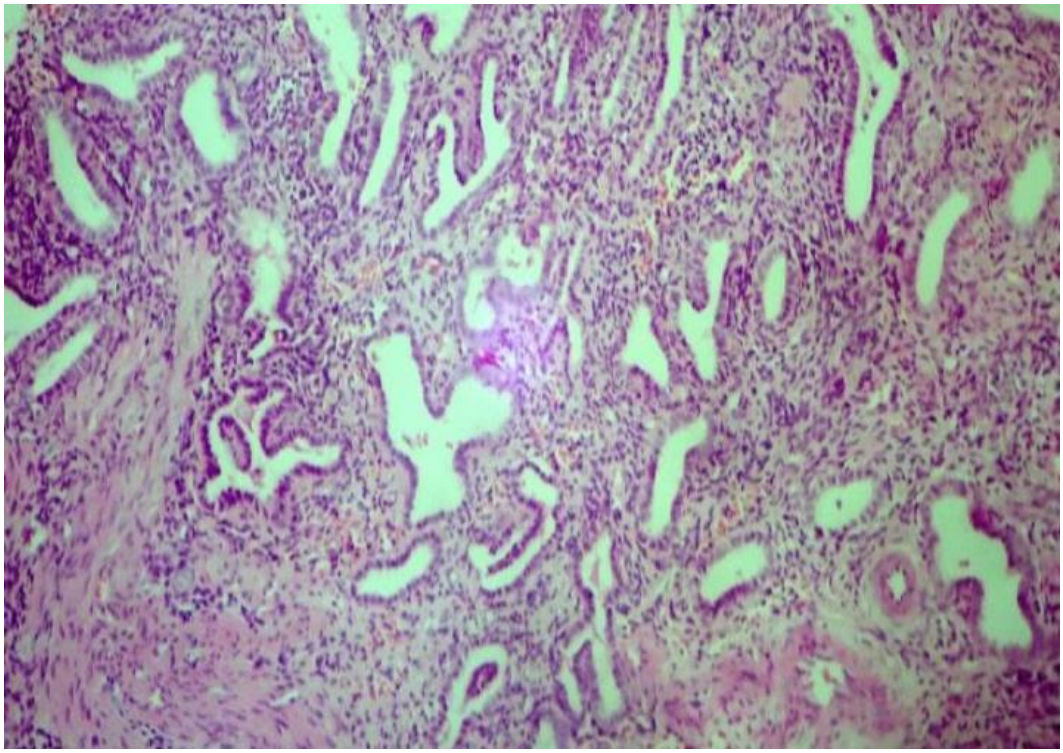


Figure ix - SIMPLE HYPERPLASIA WITHOUT ATYPIA OF ENDOMETRIUM (H3054/16)

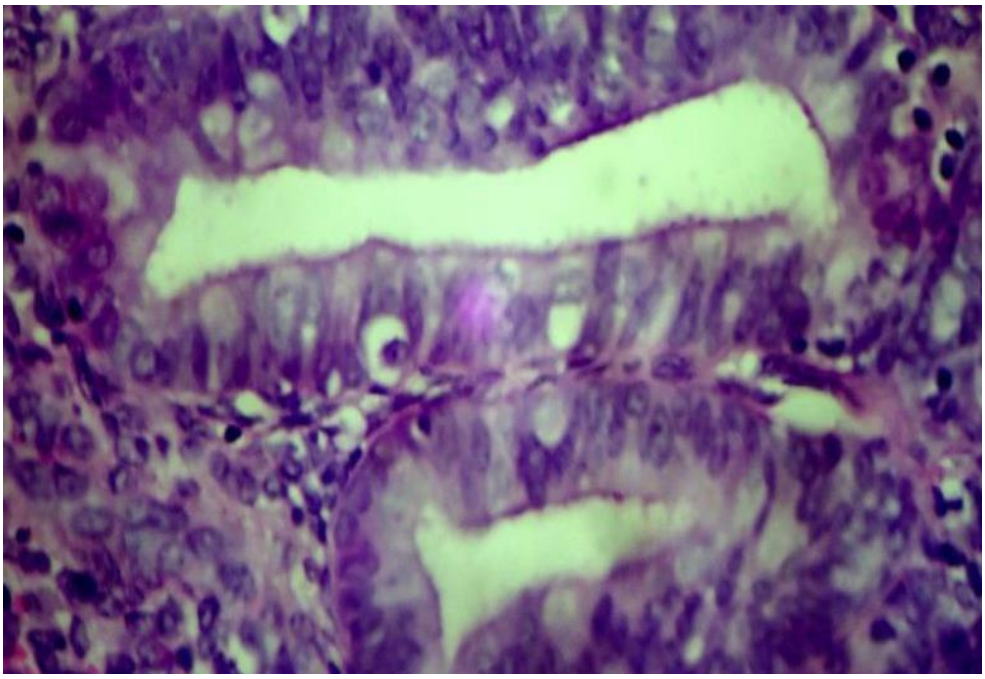


Figure x - COMPLEX HYPERPLASIA WITHOUT ATYPIA OF ENDOMETRIUM (H1270/17)

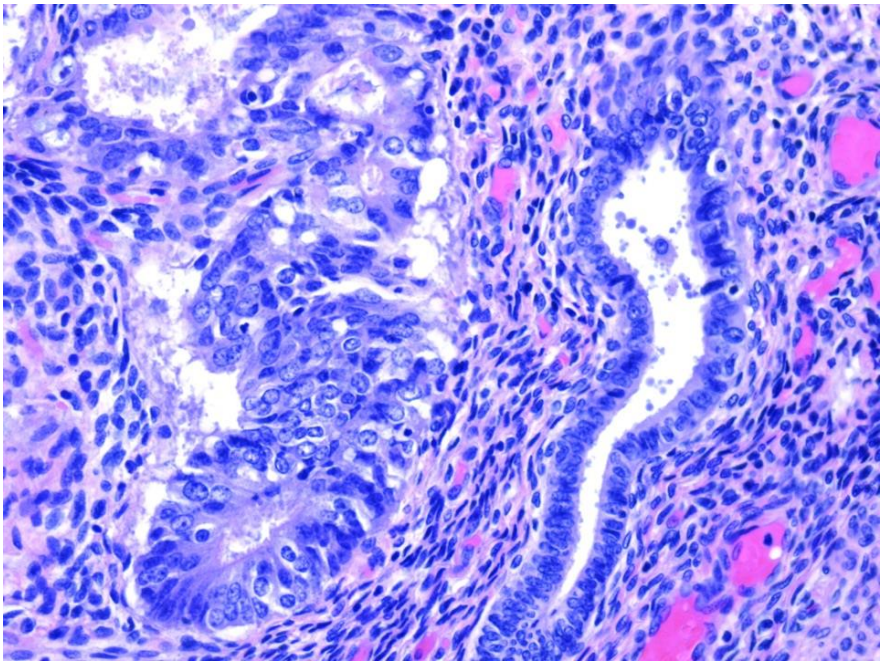


Figure xi - ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA (H973/18)

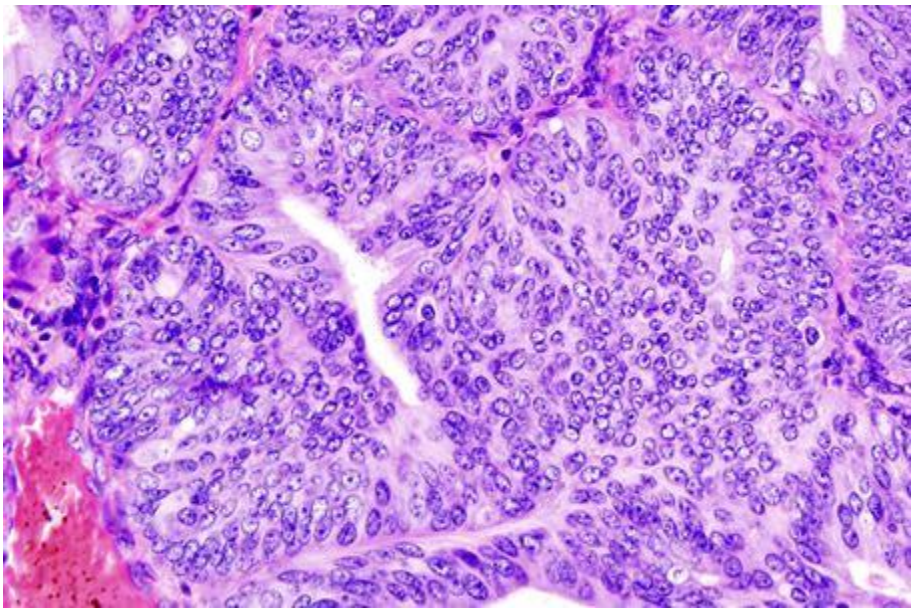


Figure xii - ENDOMETRIAL CARCINOMA (H4178/16)

Discussion

DISCUSSION

Leiomyoma of the uterus is the most common neoplasm. Many of these tumours are small and so remain undetected and are often incidental findings. Ackerman et al did a meticulous study of 100 consecutive hysterectomy specimen of which 77 revealed leiomyomas. Although Ackerman et al reported 84% of leiomyomas as multicentric, current study showed an increased incidence of single fibroids. Of 250 leiomyomas 69.2% were single and 30.8were multiple. This difference needs to be evaluated further.

Leiomyoma occurs chiefly in women during active mid reproductive years. They are present in 20 to 30% of women over 30 years of age, rising to more than 40% in those over 40 years old (Malcom. C, Anderson et al). Premenopausal patients showed an average number of myoma almost three times higher than post menopausal women (Cabrera et al 1994). In current study, only 16% were in the age group between 30 to 39 years. In this study most of the cases occurred in 40-49 age group. Only few cases were seen in post menopausal women age group. The reason for this could not be explained by the theory of enhanced estrogen stimulation causing uterine fibroids. (Muram et al). This difference needs to be further studied.

Within the uterus the leiomyoma can be intramural, subserous and submucous. Shaw et al noted these were 75%, 10% and 15% in their study group.In this study, 52.8% of cases showed intra mural fibroids. 14.4% showed in submucous region, 9.2% were subserous location. Both in submucous and

intramural region were 10% , intramural and subserous were 8%, submucous and subserous were 2.4%, all the three location were 3.2%. This finding goes in hand with the reference cited.

ENDOMETRIAL CHANGES

In the current study, thirty percent (75) of the cases reported was associated with early secretoryphase. The percent of cases associated with proliferative phase and late secretory phases were 20.8% (52) and 16% (40) respectively. The percent of cases associated with simple hyperplasia, disordered proliferative phase and atrophic endometrium were 11.2% (28), 10.8% (27) and 9.6% (24) respectively. There was one (0.4%, totally 2%) case of each - complex hyperplasia, Endometrial intraepithelial neoplasia, endometrial carcinoma.

Granjone Yanotti and Cedavd (1961) found high estrogen level in women with uterine fibroids and believed that endometrium played a role in synthesis of estrogen. According to CH Buckley, H Fox et al, these changes are insufficient to warrant a diagnosis of hyperplasia but are recognised as prolonged proliferative phase in some patients[50]. Mitotic activity continues beyond the 14th day of the cycle. But in this study, 11.2% cases showed simple hyperplasia and only 0.4% showed complex hyperplasia. According to Zhleznov BI et al., 1990, in the cases of leiomyoma, the endometrium undergoes primarily age related changes and histopathological changes. According to Land echowskij JD et al., 1982,. endometrial structures were normal in 54% of 178 patients with myoma and phases of incomplete secretion were recorded as 14.6%.

If the myometrial tumor is large, the overlying endometrium may be thinned out (CH Bukley et al 1989). The atrophic endometrium were the most constant morphological change in the presence of submucous leiomyoma (83%). Atrophy is not only due to mechanical pressure but also from the hormonal insufficiency that occurs in the post menopausal period (L.Deligdish et al Study-J. clinic Path 1970). In this study, the current study showed thinned out endometrium of 0.1 to 0.2cm in 17.4% of subserosal leiomyoma, 13.9% of the submucous leiomyoma cases and in 9.1% of intra mural leiomyoma and very few cases of post menopausal women. This should be further evaluated in detail.

Bolck et al 1961 reported endometrial hyperplasia varied between 6% and 80%. Hyperplasia is the most common changes in the endometrium with fibroid uterus (Acta Ob.Gynec. 1963). Out of 390 hysterectomy specimens, 316 cases presented with leiomyoma with different degrees of endometrial hyperplasia. Both leiomyoma and endometrial hyperplasia develop in hormonal context. The most frequently occurring type is simple hyperplasia, suggesting that there is a rare progression to highest grades.Thus, leiomyoma has a possible protective role as a target tissue which captures estrogen (Teleman S et al, 2003). Lattinen (1964) reported that hyperplasia was the most common change in the endometrium noted in the leiomyoma of uterus (J clin path 1970). In accordance with these studies the current study showed 11.2% of simple hyperplasia, 0.4% of Complex hyperplasia. These features are due to protective role of uterine leiomyoma.

In the presence of leiomyoma, the endometrium undergoes histophysiological as well as age related changes (Zhelezenov Bi et al 1990). Hyperplasia of the endometrium was recordable primarily from the women with menopausal ovarian dysfunction (Zentrabl gynekol 1982)[108]. In the current study, most of the cases were between 40 to 49 years. Of this age group, simple hyperplasia was seen in 10.6%. 22.9% showed proliferative phase. 10.6% showed early secretory phase. 40 cases belonged to age more than 50 years. Of these, 19 cases showed atrophic endometrium and 4 cases showed simple hyperplasia.

In 1961, Goranjon et al found the presence of high estrogen levels in women with uterine leiomyoma and believed that the endometrium played role in the synthesis of these estrogens[50]. Novak and wood druff (1962) described the association between leiomyoma and the an-ovulatory cycle with endometrial hyperplasia. However, in some patients, these changes are insufficient to warrant a diagnosis of hyperplasia but are recognizable as those of a prolonged proliferative phase. Mitotic activity continues beyond the 14th day of cycle (CH Bukley et al). In this study, out of 250 cases, 97 cases had LMP of 16 to 30 days and 39 cases more than 30 days of LMP. Out of 250 cases, 30 cases showed persistent proliferative phase with LMP more than 15 days. 20 cases out of 250 cases with Simple Hyperplasia had LMP of more than 15 days. This showed unopposed estrogenic action (Hyper estrogenic stage). 20 cases showing atrophic endometrium were postmenopausal women.

Adenomyosis was the commonest leiomyoma associated pathology observed in the present study with an incidence of 87 (43.50%) out of 200 cases, which is comparable to the study conducted by CarterJE, Kong I I[108] (23%).

Comparative percentage of adenomyosis in various studies.

Author	Year	Percentage
Rosario Pinto	1968	11.3
Carter JE, Kong II	1994	23
Bazot M et al	2001	33
Present study	2016	42.4

The frequency of adenomyosis which was reported in the literatures ranges widely from (5- 70%).[108]There are many reasons for this marked variations but no really satisfactory statistics had been found. The selection criteria is accountable for the myometrial specimens, and the varying histological criteria for the diagnosis of adenomyosis. This contributes to the disparity in estimation. Thus, awareness among pathologists in this condition, the number and site of myometrial samples analyzed, and the histological criteria used may all have an influence on the diagnosis of adenomyosis.

Association of adenomyosis with leiomyoma:

In the present study, leiomyoma associated with adenomyosis was noted in 22.0 % of cases. It correlates with the observation made by Loffer136 (1989, 16%) and comparatively less with other studies.

Association of leiomyoma with adenomyosis in different studies

Author	Year	Percentage
Molitor	1971	38.40
Bird et al	1972	53.00
Loffer	1989	16.0
McCausland	1992	55.00
Present study	2016	42.40

Adenomyosis in leiomyoma was associated feature seen in the present study. 106 out of 250 leiomyomas was associated with adenomyosis forming 25%. Raju GC et al (1980) reported 16%, Ben Aissia N et al (2001) had reported 62% and Thomas JS et al (1989) had noted more frequent association. Raju GC et al study in 1980 noted that association of adenomyosis in leiomyoma was the most common feature seen in reproductive period with variations in lmp. The present study also, 24% of leiomyoma in the reproductive age group were seen to be associated with adenomyosis. The common endometrial change seen is early secretory phase.

According to Zhonghua L et al 1990, there is no association of endometrial carcinoma and leiomyoma. This points to the fact, that there could be protective role of leiomyoma on endometrium hypothesized by Teleman S et al 2003. There are a few reported cases of endometrial carcinoma in association with leiomyoma. The percentage varies 0.2 to 16.2% (Dupantier N et al 2003, Tatamizawa S et al 1999, Studzinki Z et al 2000, Cabrerce J et al 1994, Studzinski et al 1998). In the present study, two cases presented with endometrial carcinoma and one case

presented with endometrial intraepithelial carcinoma. The association of leiomyoma with endometrial carcinoma should be further evaluated.

The incidence of leiomyoma is almost equal to other data available in the world literature. Many of the endometrial changes noted also correlated with findings of other authors.

Many authors worked on the endometrial changes in leiomyoma. A comparison with those studies revealed that the current observations were corrobarative except for few variations.

A striking observation was the association of adenomyosis and fibroid, 40% uterine leiomyoma was associated with adenomyosis, which substantiates the hypothesis of hormonal dependency of this tumours.

Persistent proliferative phase and simple hyperplasia were seen beyond 15 days of LMP. This means all these patients showed hyperestrogenic status, which also explains the various menstrual disturbances the patient present with. Reproductive failure may also be explained by these changes.

Though L Deligish and M Loe observed atrophic endometrium in 83% of submucous myoma, which is only a pressure change, there were significant number of cases showed proliferative phase, which could only be explained by the lower age group affected.

One case with endometrial intraepithelial neoplasm and another two cases with endometrial carcinoma were observed. There were very few cases reported

in the literature which substantiates the hypothesis of protective role of leiomyoma. However, the association between leiomyoma and endometrial carcinoma should be studied further.

Summary

SUMMARY

During the study period between November 2016 to June 2018, 250 hysterectomy specimens with myometrial lesions(leiomyoma) were taken up for studying endometrial changes and their association with adenomyosis.

1. MYOMETRIAL LESIONS(LEIOMYOMA):

a) The incidence of leiomyoma was 26.31%

b) Most of leiomyoma were seen in premenopausal women, of age group between 30 to 49 years with an incidence of 84%.Only 16% of were seen in postmenopausal age group.

c) This study showed a higher incidence of unicentric fibroid with an incidence of 69.2%

d) Most of the fibroids were present in intramural location with an incidence 52.8% followed by submucous fibroid with an incidence of 14.4%.

2. ENDOMETRIAL CHANGES :

a) The endometrium was thinned out (0.1 to 0.2cm) in all the submucous fibroids (36 cases) intramural fibroids and 20 cases of postmenopausal women.

b) 20.8% showed proliferative phase and 9.6% showed atrophic endometrium.28 showed simple hyperplasia that is 11.2%. Complex hyperplasia was seen in 0.4%.

c) Of 36 submucous leiomyomas, simple hyperplasia was seen in 11.1%.Proliferative phase was seen in 27.8%. Atrophic endometrium was seen in 13.9%.

d) In this study, 97 cases had LMP of 16 to 30 days and 59 had more than 30 days of LMP.

e) 20 cases showed persistent proliferative phase with LMP more than 15 days.21 cases showed endometrial hyperplasia with LMP of more than 15 days.

3. AGE DISTRIBUTION:

a) Most of the cases were between 40 to 49 years. In this age group, simple hyperplasia seen in 10.6%. 22.9% showed proliferative phase. 19.4% showed late secretory phase.

b) Above 50 years age group 40 cases were reported. Of these 19 showed atrophic endometrium.

4. ASSOCIATION WITH ADENOMYOSIS:

Adenomyosis was with 106 cases with an incidence of 42.4%.Out of 106 cases of adenomyosis, 26 cases showed myohyperplasia.

Malignant myometrial lesions were not obtained during the period of this study.

Conclusion

CONCLUSION

In this study, most of the myometrial lesions(leiomyoma) were seen in the 4^{th} and 5^{th} decades of life. Intramural location was seen more than other locations.

The endometrial changes seen were thinning hyperplasia(simple as well as complex) and infrequently carcinomatous change. The older group of women in this study had atrophic endometrium and relative changes.

Many of the cases had persistent hyperestrogenic stimulus.

Adenomyosis and myohyperplasia were frequent associations.

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Proforma

ANNEXURE

PROFORMA

- **Name :**
- **Age :**
- **LMP :**
- **IP no. :**
- **Date of collection :**
- **Case history :**
- **Size of myometrial lesion :**
- **Type of myometrial lesion :**
  - **Benign**
    - **Leiomyoma(subserosal/intramural/submucosal)**
    - **Adenomyosis**
  - **Malignant**
    - **Leiomyosarcoma**

Consent Form

CONSENT FORM – I

INTRODUCTION

You are invited to take part in a research study conducted by **R.RATHIKA** at **TRICHYSRM MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE.** You are invited to participate because of **MYOMETRIAL LESION.**If you take part in this studyyou will be one of the people expected to participate in study.This study is conducted under the supervision of the course instructor Dr.K.Amedkar raj.No funding has been received for this study.

PROCEDURES

If you agree to participate you will be interviewed about your complaints. The interview will last for about 20 – 30 minutes.

RISKS

To the best of our knowledge, participation in this study has no risk or harm to you. It is possible that some of the questions will make you uncomfortable but you are free to refuse to answer any questions or to stop at any time.

BENEFITS AND COSTS

You do not have to pay to participate in this study. You will not receive any direct benefits from participating in this study but we hope to gather information that will help us to evaluate the **HISTOPATHOLOGICAL ANALYSIS OF ENDOMETRIAL CHANGES IN ASSOCIATION WITH MYOMETRIAL LESIONS OF HYSTERECTOMY SPECIMENS.** You will not be compensated for participating in this study.

WITHDRAWAL FROM THE STUDY

Participation in this is voluntary. You have the right to refuse to take part in this study.

If you chose to participate you have the right to withdraw at any time without penalty or loss of benefits to which otherwise you are entitled. If there are any new findings during this study that may affect whether you want to continue to take part, you will be told about them as soon as possible. The student researchers may decide to discontinue your participation without your permission because they may decide that staying in this study will be bad for you or for any other reasons.

CONFIDENTIALITY

Protecting participants confidentiality is of the utmost importance throughout this research study. All information obtained in the interview will remain confidential. Only the student researcher **R.RATHIKA** will have access to the link between the participant name and study ID which will be stored separately AFTER the interview.

The information from the interviews will be used for research purpose only. Participants identity will not be revealed in any paper resulting from this project.

QUESTIONS OR PROBLEMS

You are encouraged to ask questions now and at any time during this study. You can reach **Dr.R.Rathika** at **TRICHY SRM MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE** for any queries. You could be contacted by the student researcher if she has any questions about your participation in this study.

CONSENT FORM - II

PARTICIPANT CONSENT FORM CERTIFICATION

I, Mrs._____ voluntarily agree for the participation as a subject of this research study by signing the consent form. The purpose and details of the study has been explained to me in my own vernacular language. I assure that I understood the above study and had the opportunity to ask questions. I may withdraw from the study anytime.

I agree not to restrict the data or results that arise from this study provided such a use is only for scientific purposes.

SIGNATURES: **DATE:**

1._____

NAME AND SIGNATURE OF THE PARTICIPANT

2._____

NAME AND SIGNATURE OF THE WITNESS

திருச்சி எஸ்.ஆர்.எம். மருத்துவமனை மற்றும் ஆராய்ச்சி மையம்

இருங்களூர், திருச்சிராப்பள்ளி – 621 105.

ஒப்புதல் படிவம்

திருச்சி எஸ்.ஆர்.எம். மருத்துவமனை மற்றும் ஆராய்ச்சி மையத்தின் நோய் குறியியல் துறையில் நடத்தப்படும் கர்பப்பை நோய்கள் குறித்த ஆய்வில் பங்கேற்குமாறு உங்களை கேட்டுக் கொள்கிறோம்.

- இப்பரிசோதனைக்கு சம்மதிப்பது உங்கள் விருப்பத்தைப் பொறுத்தது.
- இச்சோதனைக்கு கட்டணம் கிடையாது
- கட்டாயம் எதுவும் இல்லை
- பரிசோதனையிலிருந்து எந்நேரமும் விலக தங்களுக்கு முழு உரிமை உண்டு.

இந்த ஆய்வின் முடிவுகள் மருத்துவம் மற்றும் விஞ்ஞான முன்னேற்றத்திற்கு உதவும் என்று கருதுகின்றோம். இவைகளை வேறு எதற்கும் பயன்படுத்தப்பட மாட்டாது என உறுதியளிக்கிறோம்.

ஒப்புதல்

நான் திரு/திருமதி / செல்வி / .....

முகவரி . .....

நாள் . . . . . அன்று மேற்கண்ட ஆய்வுக்காக தகவல் படிவத்தினை படித்து, கேட்டு புரிந்து கொண்டு இந்த ஆராய்ச்சிக்கு அறுவைசிகிச்சை மூலம் என்னை பரிசோதனை செய்ய அனுமதிக்கிறேன். என் மனப்பூர்வமான சம்மதத்தை அளிப்பதோடு இந்த ஆய்வின் முடிவுகளை மருத்துவம் மற்றும் விஞ்ஞான நோக்கத்திற்கு பயன்படுத்த ஒப்புதல் அளிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம் ஆய்வாளர் / சம்மதம் பெறுபவர் கையொப்பம்

Master Chart

S.N	Name	Age	Histopath No	Myometrial Lesions											Endometrium									
				Leiomyoma									Adenomyosis	LMP	PP	ES	LS	DPP	SH	CH	Atrophic	EIN	EC	Others
				Location							Number													
				IM	SM	SS	IM + SM	IM + SS	SM + SS	IM + SM + SS	Single	Multiple												
1	Jerina begam	56	H 2461 / 16	1							1		1	PM							1			
2	Dhanalakshmi	35	H 2484 / 16		1						1		1	30		1								
3	Santhanamary	47	H 2486 / 16					1				1	1	10		1								
4	Saroja	60	H 2488 / 16			1					1			PM							1			
5	Sivakami	60	H 2502 / 16	1								1		PM							1			
6	Saraswathy	55	H 2577 / 16		1						1		1	PM							1			
7	Muthukannu	48	H 2578 / 16	1							1		1	28				1						
8	Kulanthaiyammal	45	H 2600 / 16					1				1	1	35			1							
9	Banumathi	41	H 2694 / 16			1					1			42			1							
10	Panjavarnam	44	H 2696 / 16	1							1			38			1							
11	Karupayee	47	H 2731 / 16	1							1		1	24				1						
12	Vembu	34	H 2732 / 16					1				1	1	26	1									
13	Umarani	42	H 2799 / 16			1					1		1	28		1								
14	Arivumalar	42	H 2806 / 16	1								1		14		1								
15	Kunjammal	50	H 2807 / 16	1								1		26		1								
16	Pappathy	62	H 2808 / 16			1					1		1	PM							1			
17	Kasthuri	40	H 2824 / 16					1				1	1	15		1								
18	Malliga	45	H 2825 / 16	1								1	1	27			1							
19	Jayarani	45	H 2841 / 16			1						1	1	23			1							
20	Kavitha	35	H 2840 / 16	1							1			16	1									
21	Poongodi	42	H 2910 / 16	1							1			48	1									
22	Vijaya	45	H 2930 / 16				1				1			22				1						
23	Sudha	34	H 2948 / 16		1						1			18	1									
24	Jegathambal	41	H 3024 / 16					1				1	1	56			1							
25	Radhakumari	46	H 3040 / 16				1				1			24				1						
26	Parameshwari	48	H 3053 / 16						1		1		1	7	1									
27	Latha	43	H 3054 / 16	1							1			10					1					
28	Parameshwari	42	H 3055 / 16							1	1			13				1						
29	Lakshmi	42	H 3115 / 16							1	1			14	1									
30	Pappi	43	H 3116 / 16	1								1	1	12				1						

31	Jothi	36	H 3156 / 16	1							1			19		1								
32	Senthamil selvi	45	H 3232 / 16				1					1		21					1					
33	Pushpavalli	40	H 3266 / 16	1							1			34			1							
34	Kala	40	H 3378 / 16	1							1			7	1									
35	jhancy	37	H 3462 / 16				1					1		35				1						
36	Mary	42	H 3480 / 16	1								1	1	8	1									
37	Lakshmi	45	H 3485 / 16				1					1		44					1					
38	Ambiga	46	H 3540 / 16				1				1			22	1									
39	Seva	60	H 3563 / 16	1							1		1	PM								1		
40	Selvi	38	H 3565 / 16				1					1		18	1									
41	Anjalai	45	H 3587 / 16		1						1			7	1									
42	Mariyayee	41	H 3637 / 16						1			1		10	1									
43	Rani	52	H 3644 / 16	1							1			PM								1		
44	Rajeswari	32	H 3646 / 16							1		1		23		1								
45	Shanthi	48	H 3648 / 16	1								1		13	1									
46	Valarmathy	52	H 3671 / 16		1						1			PM								1		
47	Eshwari	45	H 3086 / 16						1		1			36			1							
48	Anthoniyammal	42	H 3762 / 16							1		1		16				1						
49	Selvi	46	H 3793 / 16		1						1			9	1									
50	Vasantha	35	H 3795 / 16		1						1		1	46			1							
51	Parvathy	50	H 3829 / 16	1							1		1	PM								1		
52	Vijayalakshmi	45	H 3843 / 16					1			1			23	1									
53	Tamilarasi	48	H 3845 / 16	1							1			9	1									
54	Rani	46	H 3859 / 16		1						1		1	8	1									
55	Lakshmi	49	H 3895 / 16		1						1		1	34			1							
56	Saraswathy	52	H 4061 / 16	1							1		1	28		1								
57	Vijaya	36	H 4119 / 16	1							1		1	24		1								
58	Bathurnisha	38	H 4249 / 16	1							1			32					1					
59	Kalaiselvi	52	H 4279 / 16	1							1		1	26		1								
60	Amudha	46	H 4296 / 16	1							1		1	14	1									
61	Muthulakshmi	62	H 4178 / 16			1					1			PM									1	
62	Chinnammal	45	H 4244 / 16	1							1			27		1								
63	Pappu	52	H 4375 / 16	1							1			32			1							
64	Rajammal	55	H 4450 / 16					1				1	1	PM								1		
65	Umamaheswari	40	H 4411 / 16	1							1			33		1								
66	Sabiya	48	H 4482 / 16	1							1			40		1								
67	Amsavalli	43	H 4483 / 16	1							1			42			1							
68	Jehabar nachiya	45	H 4540 / 16	1							1		1	42			1							
69	Selvi	41	H 4576 / 16						1			1	1	36			1							
70	Rajammal	55	H 4450 / 16									1	1	PM								1		
71	Clara	60	H 4646 / 16				1					1	1	PM								1		

72	Amudha	39	H 4728 / 16	1							1			25		1							
73	Subarammal	49	H 4761 / 16	1							1			30	1								
74	Anjalai	46	H 4844 / 16	1							1			22		1							
75	Punitha	43	H 4903 / 16		1						1			20			1						
76	Thilagavathy	42	H 5038 / 16	1								1		16		1							
77	Latha	35	H 5105 / 16				1					1		13				1					
78	Senthamil selvi	50	H 5067 / 16				1					1		8	1								
79	Anjalai	48	H 5066 / 16				1					1		9	1								
80	Indhira	32	H 4759 / 16	1							1			34			1						
81	Manimegalai	40	H 5120 / 16	1							1			32				1					
82	Saroja	40	H 5123 / 16	1							1		1	28			1						
83	Jeenath Begam	44	H 5141 / 16	1							1			46					1				
84	Rajeswari	41	H 5144 / 16	1							1			48			1						
85	Tamilselvi	57	H 5158 / 16	1							1			PM							1		
86	Reetha	67	H 5170 / 16	1							1			PM							1		
87	Thangamani	47	H 5219 / 16	1							1			28			1						
88	Jenitha	42	H 5287 / 16	1							1			30			1						
89	Rajalakshmi	45	H 352 / 17	1								1		10		1							
90	Revathy	43	H 2 / 17	1							1			58			1						
91	Selvi	49	H 122 / 17	1							1		1	6				1					
92	Anandha gowri	45	H 158 / 17		1						1		1	44			1						
93	Arayee	35	H 227 / 17	1							1			44			1						
94	Habibu Nisha	46	H 277 / 17		1						1			28					1				
95	Jayanthi	45	H 299 / 17	1							1			15		1							
96	Kalaiselvi	42	H 760 / 17	1							1		1	42			1						
97	Rajeswari	32	H 755 / 17				1					1		38		1							
98	Banu	40	H 752 / 17	1							1		1	22		1							
99	Rajathi	37	H 735 / 17		1						1		1	14					1				
100	Nirmala	47	H 653 / 17					1				1		54				1					
101	Kogilavani	36	H 620 / 17	1								1		47		1							
102	Pushpam	52	H 607 / 17				1					1	1	PM					1				
103	Petchiammal	55	H 606 / 17	1							1		1	20		1							
104	Backiyam	50	H 571 / 17				1					1		7		1							
105	Valli	46	H 570 / 17	1							1			20		1							
106	Ambiga	40	H 530 / 17	1							1		1	22				1					
107	Tamilarasi	45	H 531 / 17	1							1			44		1							
108	Dhanalakshmi	48	H 529 / 17	1							1			60				1					
109	Andars Mary	40	H 492 / 17	1								1		34		1							
110	Kannammal	58	H 478 / 17	1							1			PM								1	
111	Maheswari	40	H 476 / 17	1							1			22				1					
112	Alagammal	51	H 460 / 17	1							1			PM							1		

113	Selvi	43	H 456 / 17	1							1			28					1					
114	Srividhya	40	H 438 / 17	1							1		1	32	1									
115	Selvi	45	H 436 / 17		1						1			22	1									
116	Malathi	46	H 419 / 17	1							1			24					1					
117	Rasammal	40	H 405 / 17	1							1			30					1					
118	Thavamani	43	H 402 / 17	1							1		1	8		1								
119	Dhanalakshmi	46	H 397 / 17	1							1		1	34					1					
120	Susila	44	H 796 / 17	1							1			40			1							
121	Jebakumari	46	H 836 / 17	1								1	1	32		1								
122	Vembu	47	H 843 / 17	1							1			38		1								
123	Mariyayee	51	H 854 / 17		1						1		1	44			1							
124	Panjavarnam	35	H 855 / 17	1							1			56			1							
125	Manjula	36	H 856 / 17	1							1			28		1								
126	Indhira Gandhi	42	H 870 / 17	1								1		30				1						
127	Radha	47	H 873 / 17	1							1			29		1								
128	Savariyayee	48	H 927 / 17	1							1			25		1								
129	Sagunthala	45	H 933 / 17	1							1		1	18		1								
130	Pappathy	53	H 949 / 17	1							1			PM					1					
131	Pattu	45	H 999 / 17	1							1		1	26		1								
132	Caroline	53	H 1030 / 17	1								1	1	PM		1								
133	Amutha	42	H 1053 / 17	1							1			14		1								
134	Jaya	55	H 1059 / 17		1							1	1	14		1								
135	Aamena	40	H 1077 / 17			1						1		26		1								
136	Anjalai	48	H 1078 / 17	1							1		1	32			1							
137	Kamala	49	H 1113 / 17	1							1		1	11			1							
138	Elanjium	43	H 1169 / 17			1					1			15		1								
139	Noorjahan	41	H 1170 / 17		1							1	1	11	1									
140	Fajhulla	43	H 1222 / 17	1								1	1	28		1								
141	Mookayee	38	H 1263 / 17	1							1			6	1									
142	Sampoornam	45	H 1270 / 17	1							1		1	42						1				
143	Mumthaj	50	H 1686 / 17	1							1		1	7	1									
144	Chithra	45	H 1683 / 17			1					1			13		1								
145	Shanthi	33	H 1666 / 17	1							1			21		1								
146	Chitra	43	H 1662 / 17	1							1			24		1								
147	Dhanaselvi	39	H 1661 / 17			1					1		1	7	1									
148	Iyyanaramma	46	H 1584 / 17				1					1		20		1								
149	Usharani	37	H 1559 / 17							1		1	1	5		1								
150	Amuthavalli	43	H 1541 / 17				1					1		25			1							
151	Saroja	40	H 1517 / 17	1							1			13				1						
152	Vellaiyammal	46	H 1507 / 17	1							1		1	24		1								
153	Vijayalakshmi	40	H 1399 / 17					1				1		28		1								

154	Bhavani	42	H 1398 / 17						1			1	1	22	1										
155	Rajakumari	43	H 1392 / 17				1					1		32			1								
156	Revathy	45	H 1379 / 17		1						1		1	30	1										
157	Thayamuthu	41	H 1358 / 17						1			1		PM	1										
158	Patchayammal	38	H 1333 / 17	1							1		1	30					1						
159	Malliga	38	H 1432 / 17	1								1		4		1									
160	Nallammal	43	H 1453 / 17					1				1		39		1									
161	Vijaya	45	H 1452 / 17					1				1		14	1										
162	Dhariamani	56	H 2912 / 17	1							1			12					1						
163	Parameshwari	43	H 2937 / 17			1					1		1	PM	1										
164	Vellaiyammal	40	H 2938 / 17			1					1		1	26		1									
165	Suba	39	H 2968 / 17	1							1		1	22				1							
166	Kameshwari	48	H 3009 / 17		1						1			34		1									
167	Jackuline Mary	49	H 3013 / 17					1				1		24					1						
168	Selvi	45	H 3016 / 17	1							1		1	23				1							
169	Lakshmi	45	H 3163 / 17					1				1	1	15	1										
170	Kannagi	46	H 3035 / 17			1					1			12		1									
171	Jothi	43	H 3160 / 17	1							1		1	24				1							
172	Kamaladevi	39	H 3211 / 17			1					1			30	1										
173	Santha	41	H 3219 / 17			1					1			25		1									
174	Ramayee	40	H 3220 / 17				1					1		15	1										
175	Selvakumari	45	H 3229 / 17					1				1	1	18		1									
176	Nirmala rani	42	H 3330 / 17	1							1		1	21	1										
177	Arulmary	40	H 3325 / 17	1							1			24			1								
178	Poonkodi	45	H 3379 / 17							1		1	1	32					1						
179	Poovalagi	45	H 3348 / 17	1								1		34	1										
180	Sagaya mary	43	H 3426 / 17		1							1	1	9				1							
181	Semila	35	H 3424 / 17	1							1			34	1										
182	Anthoniyammal	45	H 2818 / 17	1							1			30								1			
183	Gajalakshmi	45	H 2821 / 17	1							1			18		1									
184	Alphonse mary	45	H 2852 / 17	1							1			60					1						
185	Josephin	41	H 2856 / 17		1						1			9			1								
186	Dhavamani	56	H 2912 / 17		1						1			11					1						
187	Parameshwari	43	H 2937 / 17	1							1		1	PM	1										
188	Rajalakshmi	47	H 2944 / 17	1							1			24		1									
189	Amirtham	36	H 3501 / 17	1							1		1	12					1						
190	Seethalakshmi	44	H 3131 / 17				1					1		14					1						
191	Chandra	50	H 3141 / 17			1					1			PM								1			
192	Anandha valli	50	H 3156 / 17					1				1		PM								1			
193	Chinnamari	42	H 3492 / 17		1							1		22								1			
194	Anjugam	42	H 3573 / 17			1					1			25				1							

195	Sivagami	53	H 3548 / 17							1		1		23		1									
196	Vijaya	48	H 3496 / 17				1					1		33	1										
197	Sanariyammal	48	H 3972 / 17	1							1			7	1										
198	Arifa	38	H 3954 / 17	1							1			16	1										
199	Vijaya	49	H 3953 / 17	1							1		1	28		1									
200	Susila	48	H 3946 / 17					1				1	1	7		1									
201	Jacquline	38	H 3887 / 17		1						1		1	10		1									
202	Poovayee	45	H 3840 / 17	1								1		28			1								
203	Celine	48	H 3817 / 17	1							1		1	PM	1										
204	Mehathaj Begam	36	H 3757 / 17				1					1	1	20			1								
205	Susila	39	H 3748 / 17	1							1			4	1										
206	Dhanalakshmi	55	H 3745 / 17	1							1		1	40	1										
207	Shanthi	45	H 3725 / 17		1						1		1	11		1									
208	Elisabeth Rani	57	H 3675 / 17			1					1			10								1			
209	Nagajothy	39	H 3670 / 17		1						1		1	14		1									
210	Amutha	40	H 3645 / 17	1							1		1	28			1								
211	Chitra	48	H 3624 / 17	1							1			24	1										
212	Amudha	46	H 3618 / 17			1					1			60				1							
213	Saroja	43	H 3603 / 17	1							1		1	14		1									
214	Nigar Suldhana	40	H 3598 / 17					1				1	1	15		1									
215	Shanthi	48	H 3574 / 17			1					1		1	62			1								
216	Rani	40	H 448 7/ 17	1							1		1	17		1									
217	Vijaya	49	H 4471 / 17		1						1		1	24		1									
218	Shanthi	46	H 4455 / 17	1							1			26		1									
219	Chitra	45	H 4444 / 17	1							1		1	28			1								
220	Vijaya	45	H 4430 / 17			1					1		1	20		1									
221	Jegadeeswari	58	H 4426 / 17		1						1		1	PM								1			
222	Lalitha	45	H 4425 / 17				1					1		20				1							
223	Sagunthala	37	H 4366 / 17	1							1			20		1									
224	Vennila mary	42	H 4346 / 17		1						1		1	PM	1										
225	Annakili	46	H 4335 / 17				1				1		1	PM	1										
226	Jayanthi	42	H 4318 / 17	1							1		1	20	1										
227	Vigneswari	48	H 4301 / 17							1		1	1	17		1									
228	Thilagavathy	44	H 4300 / 17			1					1		1	10					1						
229	Cellapappa	42	H 4296 / 17		1						1		1	17	1										
230	Kamala	40	H 4248 / 17	1							1			64			1								
231	Rajammal	55	H 4231 / 17					1				1	1	46				1							
232	Sharulatha	43	H 4227 / 17	1							1		1	38	1										
233	Shanthi	47	H 4179 / 17		1						1		1	19	1										
234	Chitra	45	H 4159 / 17	1							1		1	26					1						
235	Amirtham	48	H 4096 / 17	1							1			32					1						

236	Rajakumari	40	H 474 / 18		1						1		1	33			1							
237	Lucas Rexceline	50	H 406 / 18	1							1			PM							1			
238	Eshwari	42	H 448 / 18				1					1		17					1					
239	Chitra	42	H 449 / 18					1				1	1	13				1						
240	Lakshmi	37	H 459 / 18	1								1		11		1								
241	Bajiriya	43	H 550 / 18		1						1		1	42					1					
242	Iruthayamary	42	H 564 / 18	1							1			PM							1			
243	Sumathy	45	H 551 / 18			1					1		1	5		1								
244	Malliga	47	H 109 / 18		1						1			28							1			
245	Ramzan Begam	38	H 667 / 18		1							1		34		1								
246	Chandra	44	H 849 / 18		1						1		1	18		1								
247	Saraswathy	37	H 851 / 18	1							1			21					1					
248	Rani	39	H 953 / 18					1				1	1	6					1					
249	Backiyam	50	H 979 / 18				1					1		PM				1						
250	Susila	45	H 973 / 18	1							1			29								1		