DISSERTATION ON UTERINE FIBROID AND ENDOMETRIAL CHANGES ASSOCIATED WITH FIBROID UTERUS

DISSERTATION SUBMITTED FOR

MD (PATHOLOGY)

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CERTIFICATE

This is to certify that this dissertation entitled **"Dissertation on uterine fibroid and endometrial changes associated with fibroid uterus"** is the bonafide original work of **Dr.K.Ambedkar Raj,** in partial fulfilment of the requirement for **MD (Branch III) Pathology** examination of the Tamil Nadu Dr.MGR Medical University to be held in September 2006.

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DECLARATION

I, **Dr.K.Ambedkar Raj,** solemnly declare that dissertation titled, **"Dissertation on uterine fibroid and endometrial changes associated with fibroid uterus"** is the bonafide work done by me at Govt. Stanley Medical College and Hospital during the period August 2003 to Febuary 2006 under the expert guidance and supervision of **Prof.A.Sundaram MD, Head of the Department,** Department of Pathology.

The dissertation is submitted to the **Tamil Nadu Dr. MGR Medical University** towards partial fulfilment of requirement for the award of **MD Degree (Branch III) in Pathology.**

Place : Chennai

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CONTENTS

INTRODUCTION

The uterus, stimulated continually by hormones, denuded monthly of its endometrial mucosa, and inhabited periodically by fetuses is subject to a variety of disorders. One among them is fibroid (leiomyoma) uterus, which is the benign smooth muscle tumour of the uterus and it is the most common of all uterine neoplasms. It seems that myoma are dependent on estrogen for continued growth, it is possible that estrogen is also a factor in endometrial changes. Thus one must anticipate the association of these two. So especially interesting is the condition of the endometrium in association with fibroid. It may show little or no departure from the normal and the histologic sequence of cyclic change may occur just as it does in the ovulatory cycle of non myomatous patients. On the other hand in a considerable proportion of case one finds an association of the non ovulatory type of cycle with myoma with frequently hyperplasia of the endometrium of more or less marked degree. This dissertation deals with the study of changes in endometrium associated with leiomyoma uterus with special reference to submucous, intramural and subserous fibroid in all Hysterectomy specimens from Govt. RSRM hospital and those are available in

department of pathology, Stanley Medical College, Chennai for the period of August 2003 to February 2006.

AIMS AND OBJECTIVES

1. To analyze the incidence of leiomyoma in hysterectomy specimens.
2. To analyze the site wise distribution of leiomyoma in uterus.
3. To analyze the histomorphological pattern of endometrium in leiomyoma uterus.
4. To study the endometrial changes in fibroid uterus on the basis of different age group.
5. To analyze associated changes in myometrium.
6. To analyze the endometrial changes in relation with LMP.

REVIEW OF LITERATURE

EMBRYOLOGY AND HISTOGENESIS

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

ANATOMY

The uterus of an adult weighs on average from 30 to 50 grams. The measurements are subject to individual variations. It's average length range from 5-7 cm. its greatest depth is 3 cms. The body of uterus comprises of an anterior and a posterior wall, fundus and the lateral margins. It contains a narrow triangular space called the endometrial cavity. The base of the triangle is the interior limit of the fundus, while the angle lies at the internal os of the cervix. The endometrial cavity communicates with the fallopian tube through the right and left cornua.

APPLIED HISTOLOGY

The histologic architecture of the body of the uterus in characterized by 3 layers

1. Serosa - Outer layer
2. Myometrium - Middle layer
3. Endometrium - Inner layer

The serosa is identical with the peritoneum

The myometrium is composed of fibres that are arranged interlacing bundles between the strands of interstitial connective tissue.

Endometrium consists of endometrial glands and stroma and characteristic changes takeplace in the endometrium during different stages of menstrual cycle.

HISTOLOGY OF ENDOMETRIUM

Endometrium composed of two layers. They are stratum basalis, the basal thin layer and stratum functionalis, the superficial thick layer. This layers formed by glands, held together by connective tissue called as endometrial stroma and lined on the surface by simple columnar epithelium. The stroma consists of embryonic type, highly cellular connective tissue containing 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. The arteries from the arcuate -> radial -> straight artery enter into the basal layer then as they progress more apically they becomes tortuous finally giving off numerous branches. The capillaries end in capillary bed that includes lacunae – thin walled dilated segments at the superficial portion of stratum functionalis. (Ross et al, 1995) The surface epithelium is less responsive to hormonal stimuli. The functionalis layer is more responsive to hormonal stimuli. The basal layer does not respond to hormonal stimuli.

THE GLANDULAR EPITHELIUM

The glandular epithelium is a single layer of columnar epithelial cells. Their height varies depending upon the functional state, from 6μ postmenstrual to 20μ at the end of proliferative phase. During the proliferative phase the nuclei of glandular cells are enlarged and have a dense chromatin. Between the 10^{th} and 16^{th} day of the cycle their DNA content reaches its maximum (Voker, 1951). During the secretory phase the nuclei becomes round, vesicular. The nuclei contain abundant RNA. The RNA of cytoplasm reaches its greatest concentration after ovulation. The nucleoli of early proliferative phase are finely granular and compact. They enlarge as midcycle is approached and may reach 2.8μ in diameter (Fassake et al, 1965). During the first week of the secretory phase the nucleoli contains a characteristic tubular or meshwork like structure, the nucleolar channel system which is embedded in an electron dense matrix and contains RNA. It serves the exchange of protein between nucleolus and cytoplasm for enzyme synthesis (Dubauszky and Pohlmann, 1960, Armstrong et al, 1973). The channel system apparently occurs only in human endometrium and

seems to depend on adequate levels of progesterone. It can be demonstrated shortly before ovulation by Electron microscopy (Feldhaus et al, 1977).

During the proliferative phase the cytoplasm is unusually rich in RNA as disclosed by histochemical techniques (Wislocki and Dempsey, 1945) or by fluorescence microscopy (Dallenbach and Dallenbach – Hellweg, 1968). The cytoplasm especially 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, and they are stabilizing the rigidity of cells prior to nidation (Clyman et al, 1982). At the base of the cell near the first aggregate of glycogen the mitochondria multiply and enlarge with the onset of secretory phase. Abundant basal secretory granules then collect around smooth endoplasmic reticulum. As glycogen, mucopolysaccharides and proteins accumulate at the lower pole of the nucleus to form cloudy or granular deposits, the large mitochondria nearby swell to giant size and may reach 7μ in diameter. On the 17th day of the menstrual cycle glycogen is found scattered throughout the cytoplasm, with the onset of secretion on 19th and 20th days the cytoplasm along the luminal surface sends out enlarged microvilli filled with secretory products. Shortly

thereafter the apical portion of the cell is discharged into the lumen. Thus, the epithelial cell expels their products by apocrine secretion thereby becomes smaller. The glycogen thought to serve a complex function involving more than pure glandular secretion (Sakuma, 1970).

Occasionally ciliated columnar cells found among the glandular epithelial cell (Mandl, 1911). The ciliated cells initially lie against the basement membrane and because of their abundant translucent cytoplasm can be readily recognized as a “clear cell”. Their rounded nucleus is generally located above those of the neighboring epithelial cells (Feyrter and Froewis, 1949) ‘clear cells’ are possible precursor cells in the proliferative phase and in glandular cystic hyperplasia. Fully developed ciliated cells are most numerous around midcycle and in hyperplasia of endometrium (Maddi and Papanicolaou, 1961).

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 earlier, in large amounts and remains longer than it does in the glandular epithelium. The superficial epithelium differs from glandular epithelium functionally. Its secretion is important for the adherence and

implantation of blastocyst. As revealed by Scanning Electron Microscopy, the ciliated cells accumulated around the mouths of the glands (Hafez et al, 1975). During the secretory phase the cilia degenerate and as the apical surface of the cell continues to bulge into the uterine cavity, the size and number of its microvilli decrease (Johannission and Nilsson, 1972).

THE STROMAL CELLS

The endometrial stroma consist of pluripotential mesenchymal cells, which at the beginning of the menstrual cycle are uniformly spindle shaped, poorly differentiated, and joined to one another by cytoplasmic processes. The cell lie firmly anchored within a delicate network of reticulin fibers. Their elongated nuclei have abundant chromatin. At the beginning of the menstrual cycle the cytoplasm of the cells forms a narrow rim around the dark nuclei. Near the end of the proliferative phase the nuclear substance becomes less dense, the nucleoli grow larger and more conspicuous, and the nuclear membrane becomes wrinkled. The RNA accumulates in the cytoplasm of the more superficial stromal cells, and their smooth and rough endoplasmic reticulum expand. The Golgi apparatus and mitochondria remains

poorly developed. Microfibrils of collagen become apparent, not only within the cell but also outside of them (Wetzstein and Wagner, 1960).

During the secretory phase the mitochondria and smooth endoplasmic reticulum increase in number and the Golgi apparatus enlarges. Vacuoles and granules begin to appear in the expanding but shortened microvilli. From the 20th day of the cycle onwards, glycogen and glycoproteins in diffuse and granular form can be demonstrated in the cytoplasm of the stromal cells with Electron Microscopic and histochemical methods (Mckay et al, 1956). Some stromal cell contains fine lipid droplets (Aschheim 1915) which, appears after estrogen stimulation. When the lipid accumulates in large amounts the stromal cell may reach the size of decidual cells and acquires a foamy cytoplasm.

Towards the end of the secretory phase there is accumulation of endometrial granulocytes. These cells are smaller than decidual cells have a crenated nucleus (Nordquist, 1970) and contains relatively large lysosomal granules (Hamperl, 1954, Hellweg, 1954), originally thought to be derived from stromal cells (Dallenbach – Hellweg, 1981) and to secrete a protelytic hormone – relaxin (Dallenbach & Dallenbach – Hellweg, 1964), it has now been shown that the endometrial

granulocytes are, a population of large granular lymphocytes, probably derived from bone marrow, which have natural killer (NK) characteristics (Bulmer et al, 1987). They play a role in successful implantation and placentation (Ritson and Blumer, 1987). These cells contain phloxinophilic granules in the cytoplasm (Hamperl, 1954, Hellweg, 1954). These cells also called as stromal granulocytes or endometrial granulated lymphocytes. They expresses CD59 & CD69 postivity.

OTHER CELLS IN ENDOMETRIUM

Lymphocytes appears frequently in non – inflamed endometrium. Lymphoid follicle in endometrium not unusual (Monch, 1918). Histiocytes and mast cells also found in the endometrium. Plasma cells and eosinophils appears very rarely (Feyrter, 1957).

THE RETICULIN FIBERS

The reticulin fibers distribution varies in the endometrium. The stroma of the basalis and the isthimic mucosa remains uniformly dense. The fiber content of the functionalis layer fluctuates during the menstrual cycle (Hormann, 1908, Hoffmeister and Schulz, 1961). With the light microscopy only occasional delicate reticulin fibers seen during

the first 8 days of the proliferative phase. As ovulation approaches, these fibers become denser and thicker. By the 4th week of the cycle, the fibers enmesh each predecidual cell and form a dense network around the glands and the spiral arterioles. Later when progesterone decreases, the reticulin fiber disintegrates. As a result the glands separate from stroma and stromal cell dissociate from one another. From the appearance and quality of reticulum network the functional state of endometrium can be evaluated (Vaczy and Scipiades, 1949).

THE GROUND SUBSTANCE

The ground substance of the endometrium bathes the cellular and fibrous components of endometrium. In the early and mid proliferative phase it chiefly contains high molecular neutral and acid mucopolysaccharides. In the late proliferative phase the ground substance begin to resolve into subgroups of low molecular size. As the time for implantation approaches in the midsecretory phase it becomes oedematous. During 4th week of menstrual cycle high molecular, neutral and acid mucopolysaccharides reaccumulate, in the compacta and around the spiral arteriole. These changes are necessary for implantation of blastocyst.

THE VESSELS

The vessels of the stratum functionalis differ from vessels of other organ and tissues by their unique structure, their sensitivity to hormones and their ability to respond quickly to such stimuli (Ramsey, 1955, Nieminen, 1962). In contrast, the vessels of stratum basalis are influenced little by hormonal changes of the cycle. The spiral arterioles of the functionalis that branch from the arteries of the basalis finally attain the upper portion of the endometrium at the end of proliferative phase. Progesterone stimulates the vessels to grow larger and longer, hence leading in their tortuosity. Such changes are especially evident during the second half of the secretory phase when the ratio of the height of endometrium to the length of the spiral arteries is 1:15 (Markee, 1950). The arteries undergo intense spiraling because they grow faster than the endometrium. Their wall, thin in the early proliferative phase grows progressively thicker (Wiegand, 1930, Farrer – Brown et al, 1970). The lining endothelial cells, originally flat, swells and soon contain large, vesicular nuclei (Keller, 1911). The capillaries of the functionalis also respond to cyclic variation of the ovarian hormones. They branch and pass just beneath superficial epithelium,

there it become largest in premenstrual phase and in decidua of pregnancy. They form lacuna like sinusoids called as anastomosing lacuna of Schmidt - Matthiesen (Schmidt – Matthiesen, 1962).

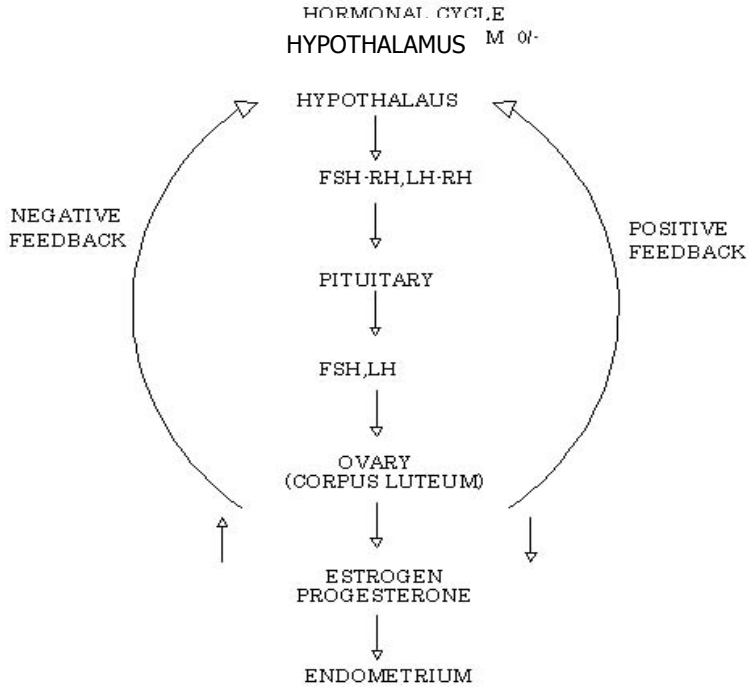
The veins of stratum functionalis respond to the hormonal stimuli of secretory phase, as other vessels (Küstermann, 1930). The venous network of the endometrium is strikingly dense. They form thin walled "lakes" beneath the superficial epithelium.

PHYSIOLOGICAL ACTION OF HORMONES ON ENDOMETRIUM

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

HORMONAL CONTROL OF OVULATION

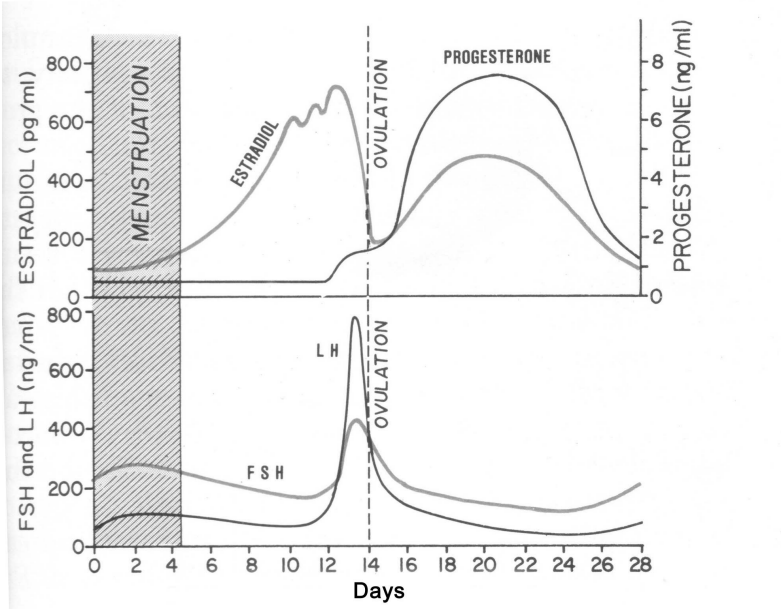
Ovulation depends upon complex interrelationship of hypothalamus, pituitary and ovary. The gonadoprophin releasing hormones (FSH / LH – RH) carried in the hypophyseal vessels to the anterior pituitary, stimulates the synthesis and release of FSH and LH into general circulation. These hormones are necessary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



At about midcycle there is an additional surge of LH release which causes the FSH primed follicle to rupture and discharge the ovum. The ruptured follicle is then transformed into a corpus luteum

which synthesize progesterone and estrogen. These steroid hormones of ovary inhibit the ovarian stimulation by gonadotrophin by negative feedback in Hypothalamo – pituitary axis. If fertilization does not occur, the corpus luteum remains transient; involutes; ovarian hormone decreases in quantity and menstruation follows. The hypophysis resumes their function and the cycle repeats itself.

Hormonal levels in normal menstrual cycle



ENDOMETRIAL STEROID RECEPTORS

The steroid hormones though diffuse into all cells; they trigger their activity through specific receptor sites on the target cells. From the receptor they are carried to the nucleus and to genes to induce

transcription and translation resulting in cell proliferation and differentiation (Gorski and Gannon, 1976).

In the stratum functionalis, the receptors for estrogen and progesterone fluctuate during the menstrual cycle (Bayard et al, 1978). The estrogen receptor when unoccupied by estrogen in the nucleus loosely bound in the monomer state. With estrogen binding, activation involves the formation of dimer (Scholls, 1984). One aspects of activation is an increased affinity for estrogen. Increase in affinity is called positive cooperativity, which increases the receptor's ability to respond small changes in the concentration of hormone. The mechanism of action is same with progesterone (Edwards et al, 1969). The concentration of estrogen and progesterone receptors is higher in the fundal region than in the middle and isthimic portion of the uterus (Kauppila et al, 1982). The basalis layer shows constant receptor number and binding is independent of the cycle phase.

The hormonal effect on epithelial, stromal and endothelial cells is mediated by estrogen receptor (E_2 R) and progesterone receptor (PR) (Katzenellenbogen, 1980), also the regulation of EGF receptor content is achieved by ovarian hormone secretion (Ferenczy, 1994). The receptors synthesised in the cytoplasm transported into the nucleus by a dimer of

heat shock protein (hsp – 90). With the formation of hormone receptor complex hsp – 90 dissociates. In the early proliferative phase, estradiol receptors gradually increase. The progesterone receptors are slightly fewer than estrogen receptor.

In the late proliferative phase the concentration of total estradiol receptors increases. The cytoplasmic receptors increase greatly, correlating with the surge of plasma estadiol. After ovulation the total estradiol receptor decreases rapidly in the early secretory phase.

ESTROGEN

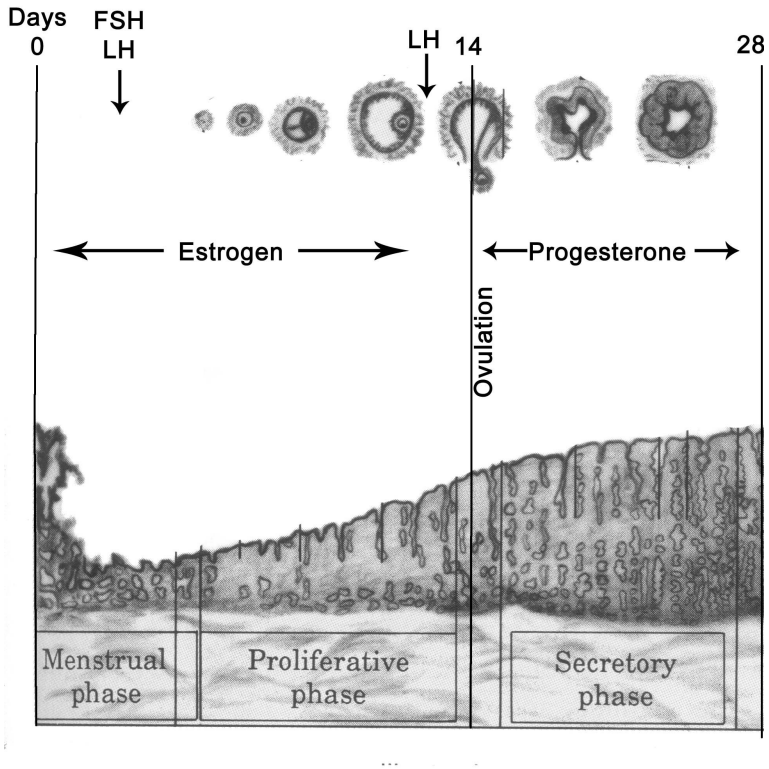
In contrast to other steroid hormones minute amount of estrogen are very potent, capable of producing rapid and significant changes in the target cell. In endometrium both stromal and glandular cell responds briskly to the estrogen. Estrogen regulates the amount of genetic material available for transcriptional results in cell proliferation seen as mitosis. The first change in the glandular and stromal cell of endometrium is the increase in RNA in the nuclei and nucleoli, followed by increase in the cytoplasmic RNA (Davidson, 1965). Finally with the secretion of progesterone, the endometrial cells cease to proliferate.

PROGESTERONE

In the human endometrium the first evidence of progesterone effect is detectable with the light microscope after 36 hours. The changes are clearing of the nuclei of glandular epithelial cells and appearance of glycogen granules at the base of the glandular epithelial cells. In Electron Microscopic studies, giant mitochondria containing DNA near the glycogen granules found (Merker et al, 1968). The progesterone stimulates the mitochondria to synthesize protein. Later in the menstrual cycle under the influence of progesterone, a nuclear channel system develops. Mitotic activity ceases. The glandular cell produces glycogen, neutral and acid mucoploysaccharides and lipids. In the 2nd week of the secretory phase the stromal cells differentiate into large predecidual cell.

THE NORMAL MENSTRUAL CYCLE

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



However, Noyes et al in 1950, first described in detail on how "to date endometrium" from histologic criteria, that is on how to diagnose how far an endometrium has developed in the menstrual cycle, from characteristic histological changes that are known to 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 :

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

PROLIFERATIVE PHASE

The endometrium regenerates from the basal layer and that part of the functional layer, which remains after menstruation. The epithelium rapidly covers over the denuded surface. Mitotic activity is not much in evidence in the early stages of regeneration. The initial resurfacing occurs independently of hormonal stimulus. The normal proliferation lasts about two weeks. But the time taken for the development of follicle varies from women to women and between cycle to cycle. It is therefore impossible to date the proliferative phase with any accuracy and it is divided into early, mid and late proliferative phase. In the early stages the glands have a low columnar epithelial lining measuring 6μ in height and a simple tubular appearance. There is evidence of mitotic activity both in the glands and in the stroma. The stroma composed of spindle cells and somewhat loosely packed.

In the mid proliferative phase the glands continue to elongate and the stromal edema develop. The elongation of the glands outstrips the stromal edema and consequently the glands become tortuous in appearance. In the late proliferative phase the stromal edema subsides and the tortuosity of the glands further increases. The mitotic activity is maximum in the glands and stroma, corresponding with the preovulation peak of the estrogen. The glandular epithelium shows pseudostratified appearance due to heaping up of the columnar epithelium. The glandular cells measure 20μ in height. The lumen appears distended. Small amount of glycogen vacuole is found in the cells. Nucleoli in the glandular cells become more prominent as the proliferative phase progresses. The individual stromal cells show little change over the period other than growth and appear to contain little cytoplasm in H & E sections (naked nuclei appearance). The cell remains well anchored in the reticulin network.

SECRETORY PHASE

Secretory phase is divided in to three phases

1. Early secretory phase
2. Mid secretory phase and

3. Late secretory phase

In the glandular epithelium subnuclear vacuoles occur after 36 – 48 hours after ovulation. It is regarded as one of the early sign of ovulation, when the majority of the cells show vacuolation. During 16 -19 day of cycle the secretory material of the subnuclear vacuole gradually moves to the apical pole of the cell and nuclei takes up a basal position. By the 16^{th} day of cycle the glands have lost their pseudostratification. Mitotic activity is still apparent and continues in the glands for some 2 – 3 days after ovulation and slightly longer in the stroma. The progesterone secretion makes the cell to lose their ability to divide. So, mitosis is absent after 19^{th} day. During ovulation the epithelial cell expresses B72 and 32 very late antigens – 1. (Ferenczy, 1994)

The secretory material accumulates at the apical poles of the cells and protrudes as blunt projections into the gland lumen, becoming maximal by day 21 of the cycle. As the material is shed by the apocrine method, the epithelial surface assumes a more irregular shaggy appearance and secretory material dilates the gland lumens. Secretory activity continue for several days after ovulation and then, if pregnancy does not ensue, decline after day 22. The pattern of secretory activity varies in different part of endometrium. The glands begin to show involutional changes and there is inspissation or gradual disappearance

of luminal secretion. The glands progressively collapse and papillary tufts of epithelium project into the lumen, giving the characteristic saw toothed appearance.

There after the gland show variety of degenerative changes with ragged epithelial cell borders and the appearance of apoptosis and giant autophagocytic lysosomes. During the second half of the secretory phase the stroma shows typical changes. If pregnancy has not ensued, the corpus luteum begins to involute and there is fall in plasma progesterone levels. The estrogen levels which show a temporary fall after ovulation, reach a second peak by day 21 and 22. Stromal oedema begins apparent during this time of maximal estrogen stimulation. Increased level of estrogen associated with vascular endothelial swelling and increased fenestration of the endothelial capillary lining. These changes are mediated by prostaglandin F_2 (PGF2) and prostaglandin E_2. (Ferenczy, 1980, Smith et al, 1983).

The edema subsides by 23rd day. The spiral arteriole becomes more prominent. This is due to increase in length of the arterioles and in part to the predecidual changes which occurs in the stromal cell immediately adjacent to these vessels. The stromal cells enlarge and assume a polygonal shape with small rounded nuclei; the cytoplasm is copious and shows the accumulation of glycogen and lipid. These

changes allow the separation of the endometrim. During the last two days of the cycle prior to menstruation the stroma shows accumulation of endometrial granulocytes.

MENSTRUATION

At the end of each cycle if pregnancy has not occurred a proportion of the endometrial lining is shed. This together with blood inspissated secretory products and other debris makes up the menstrual flow. Usually lasting for some four days, the process is related to hormonal levels. Both estrogen and progesterone become deficit in the later stage of the cycle (Zuckerman, 1949). The hormones also cause loss of fluid in endometrium and it shrinks (Markee, 1950), approximately 30% of the bulk being lost. This shrinkage results in further coiling of the spiral arteriole with further reduction in blood flow. The shrinkage causes the glands to pack more closely together and gives an impression of increased cellularity which is heightened by the endometrial granulocytes and leucocytes accumulating at this stage. In the few days immediately preceding the menstruation there is constriction of the spiral arteriole brought about by shrinkage of endometrium with blanching of the overlying epithelium. It has been suggested that the triggering effect on spiral arteriole is due to a

reduction in the circulating progesterone-estrogen concentration below some critical level (Zuckerman, 1949 loc cit). After a time the vessels dilates and the damaged vessel wall allows the red blood cells to pass through. As a result small haematoma collect beneath the surface, raising blebs. When the necrotic epithelium is shed the blood comes to lie directly on the surface. The shedding of endometrium starts superficially and proceeds to the deeper layer and rapid disintegration then takes place. The endometrium usually shed in piecemeal fashion and occasionally shed in larger fragments. The tissue is heavily infiltrated by acute inflammatory cells.

THE MENSTRUAL CYCLE VARIATION

The variation in cycle length in different women is considerable, the mean is 29.6 days. There is a tendency for mean cycle length to decrease with age from 30.1 days at the age 20 – 27.2 days at the age 40 (Treloar et al, 1967). Any menstruation outside this limit, any bleeding at other times in the menstrual cycle and any acyclical, premenopausal bleeding are considered as abnormal. The duration of menstrual bleeding also varies in different women from 2 to 7 days with a mean of 5 days (Guillebaud and Bonnar, 1978), but any menstruation lasting 8 days or longer should be regarded as excessive. The average menstrual

blood loss is about 80ml per cycle (Hallberg et al, 1966) and blood loss more than that considered abnormal.

DYSFUNCTIONAL UTERINE BLEEDING

The endometrium responds to every alteration in hormonal balance that occurs as a result of absence of hormone, deficiency of hormone, or excessive secretion of hormone. Alteration in the hormone status either due to primary-intrinsic ovarian abnormalities or secondary-disturbances in the hypothalamo- pituitary–ovarian axis such hormonal changes produce arrest in follicular maturation at different stagers of its development and results in morphological changes that corresponds to the stage of maturation at which the follicle become impaired. Follicular arrest will lead to lack of endometrial stimulation, when the injury occurs during the hormone secreting stages of follicle or corpus luteum. When the injury results in arrest of follicular regression with anovulation or prevents involution of the corpus luteum the effect on the endometrium will be that of hyper stimulation.

Hormonal imbalance may be due to deficiency of one hormone or normal state of one and excessive amount of other. This imbalance induces morphological changes in the endometrium. These

morphological changes can be differentiated with additional factors like history and general examination of patient and the diagnosis can be arrived with the light microscopic examination of endometrial samples.

Anovulatory disturbances

Endometrial atrophy

Deficit Proliferation

Irregular Proliferation

Estrogen Withdrawal bleeding

Ovulatory disturbances

Deficient Secretory state

Deficient Secretory state with co-ordinated delay

-True delay

-Apparent delay

Deficient Secretory state with dissociated delay

Progresterone receptor deficiency

Irregular shedding

Dysmenorrhoea Membranacea

ANOVULATORY DISTURBANCES

ENDOMETRIAL ATROPHY

During the reproductive year endometrial atrophy is always abnormal, and indicates a complete lack of endometrial response to ovarian hormones. This may be caused by primary absence or surgical resection of ovaries or their functional eradication by radiotherapy or chemical toxins, by severe damage to the controlling pituitary hypothalamic centre or by local refractoriness of the endometrium to the ovarian hormones. The endometrial refractoriness associated with normal ovarian function and a regular biphasic menstrual cycle (Plotz, 1950; Eufinger 1952), is termed as the ‘silent ovulation’ of Stieve (1952). This condition is due to an inability of the endometrial cells to produce hormone receptors. Cellular proliferation and differentiation cannot takes place if either the hormone or the receptor is not available.

Histologically, the epithelial and stromal cells are small even at higher magnification. Glands can hardly be distinguished under low magnification or at best resembles capillaries. They are small very sparse and lined by low cuboidal epithelial cell having small, round nuclei with dense chromatin. The cytoplasm is scanty, and mitosis is lacking. The stroma consists of small, densely packed spindle cells.

The entire height of endometrium is very much reduced and the stratum basalis cannot be recognized. In extreme instances no glands remain and the flat epithelium of the surface is separated from the myometrium by a stromal layer just a few cell thick. The blood supply is minimal and no spiral arterioles can be made out. The atrophy of the endometrium is sometimes associated with the development of large dilated venules situated superficially under a thin endometruim. These venules may rupture and are probably the cause of uterine bleeding.

DEFICIENT PROLIFERATION

If a growing follicle, does not reach maturity because of central hypogonadotrophism or ovarian damage and remains functionally insufficient, too little estrogen will be produced with two consequences.

1. The LH peak will not develop and LH levels will remain low because of insufficient feed back stimulation, due to the diminished concentration of FSH in the early phase. Thus ovulation dos not take place.
2. The endometrium will not proliferate correctly, because it is under stimulated. Although the LH concentration is too low to

induce ovulation it may cause sporadic luteinizaltion in the sufficient follicle.

Histologically, the endometrial glands and stroma show a distinct retardation of growth. The glands remain narrow and straight. Their lining epithelium is low columnar and contains chromatin rich nuclei in single rows with scanty cytoplasm. The estrogen receptor content is low. Mitosis is rare. The stromal cells are small, spindle shaped, poorly differentiated and densely packed. The general height of the endometrium is moderate, with its surface slightly irregular because of variations in growth. The regions close to the blood supply are slightly more advanced in their proliferation than the neighboring more peripheral regions. This picture remains consistent throughout the menstrual cycle with little variation. Occasional basal vacuoles may found, indicates focal abortive secretion induced by little amount of progesterone produced in luteinized regions of the insufficient follicle.

IRREGULAR PROLIFERATION:

Although a follicle has normally matured, ovulation may not take place, either because of a central defect in LH stimulation or hyperstimulation with FSH, or because of an ovarian damage. The unruptured (Persistent) follicle will continue to produce estrogen beyond the proliferation phase for a varying number of days and will then slowly regress, resulting in anovulatory shedding which may occur at the same time as menstrual shedding, or may be more or less delayed,

depending upon how long the follicle persist. Irregular proliferation may also develop when previous repeated anovulatory cycles have built up a relative estrogen predominance, which increases with each successive anovulatory cycle.

Histologically, the growth of the glands and stroma clearly exceeds that of the normal proliferative phase. The glands vary in their distribution, lying either closely packed or widely dispersed, and their diameters differ considerably. Some may be lined by a pseudostratified or even stratified tall columnar epithelium. On immunohistochemical examination the nuclei of proliferating epithelial cell show strong positivity for estrogen receptors. The stroma is composed of densely arranged spindle cells and irregularly edematous. The spiral arteriole remains underdeveloped: instead thin walled venules are found. Although the height of the endometrium varies considerably, it is usually increased, often markedly so.

If the ovulation takes place rarely, the basal vacuoles seen in the highly proliferating glands, which are close to the blood supply. In these cases a delayed and deficient secretion had occurred that never developed as fully as in a normal menstrual cycle. In instance sporadic luteinization may occur in part of the granulosa cells of the persistent

follicle in a similar manner as in the insufficient follicle. These luteinized cells may also produce small amounts of progesterone, which can induce abortive secretion with small basal vacuoles developing in the glandular epithelium. These can be differentiated from those of a truly delayed ovulation by their small size and scanty number. If an unopposed stimulation of estrogen persist then the irregular proliferation, gradually progress to a simple (Cystic) glandular hyperplasia or to atypical hyperplasia.

OVULATORY DISTURBANCES

THE DEFICIENT SECRETORY PHASE

This entity encompasses a variety of disturbances in corpus luteum function of central or ovarian origin with or without preceding abnormal follicular development. Some of these syndromes can be precisely recognized morphologically as they specifically produce changes in the endometrial structure.

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 lutenization 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 preceding follicular persistence with delayed ovulation. The associated secretory phase is of normal length or may show an early breakdown. In still other instances, the corpus luteum insufficiency is preceded by an impaired follicular development with inadequate stimulation of the granulosa cells which may be caused by insufficient FSH secretion in the early follicular phase. In these circumstances, progesterone cannot fully act on the deficiently proliferated endometrium. Furthermore the luteal phase is not only deficient but often also truly or apparently shortened (Strott et al, 1970, Jones, 1973 and 1975, and Sherman and Korenman, 1974). An apparently short luteal phase may result from early ovulation after short and deficient proliferation. On the other hand, the secretory phase may be either truly delayed after normal ovulation or apparently delayed following delayed ovulation.

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

PROGESTERONE RECEPTOR DEFICIENCY

A deficient secretory phase is, found in women with a properly timed ovulation and a normally functioning corpus luteum (Laatikainen et al, 1983 loc cit and Spirtos et al, 1985). These patients have a local deficiency of progesterone receptors and, consequently, not only

endogenous progesterone (Cooke et al, 1972), but also therapy with progesterone has no effect on the endometrium.

ENDOMETRIAL HYPERPLASIA (STANLEY J. ROBBOY ET AL)

The endometrial hyperplasias are a heterogeneous group of proliferative disorders. A confusing multiplicity of descriptive terms and a variety of largely unsatisfactory classification hinders a full understanding of their nature.

The hallmark of hyperplasia is an increased amount of glandular tissue relative to stroma, with concomitant architectural and sometimes cytological changes.

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

W.H.O. CLASSIFICATION OF ENDOMETRIAL HYPERPLASIA

Endometrial Hyperplasia

Simple

Complex (adenomatous)

Atypical Endometrial Hyperplasia

Simple

Complex (adenomatous)

ETIOLOGY

Endometrial hyperplasia is generally thought to result from excessive stimulation by estrogens.

HITOLOGICAL FEATURES OF SIMPLE HYERPLASIA

General

Diffuse changes throughout endometrium

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

Glands

Architectural features

Variation in size and shape

Small to large and cystically dialated

Minimal and focal crowding

Minimal branching with infoldings and outpouchings

No complex angularity

Cellular features

Abundant and cellular epithelium

Ciliated cell change common

Pseudostratification

Nuclear features

Oval and elongaged

No significant variation in size or shape

Evenly dispersed chromatin

Small, inconspicuous r.ucleoli

Variable mitotic activity

Stroma

Abundant and cellular

Small, oval cells with scanty cytoplasm

Mitotic activity in stroma

Prominent superficial venules

Inconspicuous spiral arterioles

HISTOLOGICAL FEATURES OF COMPLEX HYPERPLASIA

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 feature

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

HISTOLOGICAL FEATURES OF SIMPLE ATYPICAL HYPERPLASIA

General

Architectural changes diffuse throughout endometrium

Cellular changes 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

Variation in 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 aeterioles

HISTOLOGICAL FEATURES OF COMPLEX ATYPICAL HYPERPLASIA

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→hypochromasia

Variable mitotic activity

Stroma

Scanty and inconspicuous

Dense and cellular

LEIOMYOMA (FIBROID)

Leiomyoma uterus are the most common tumours of uterus and that of female pelvis. They are also the most common cause of hysterctomy world over (telinde et al). 52 percentage autopsy studied have shown the approximately 20% woman over 30 harbor uterine myomas of various sizes (Novak et al)

Leiomyomas are benign tumors composed mainly of smooth muscle cells but also varying amounts of fibrous tissue..

INCIDENCE

It's impossible to determine the exact incidence of these tumors. They present i.e. 20-30% of women over 30 years of age, rising to more than 40% in those over 40 years old (malcomc. Aderson et al)

AGE

Leiomyomas occur chiefly in women during mid reproductive years. They have been reported on rare occasion in young girl (augensen-1818). Premenopausal patients showed an average number of myoma almost three times higher than post menopausal women (Cabreraj et al 1994)

RISK FACTORS

Age: as age at menarche decreases, there is an increased rise of two to threefold, post menopausal women have a 70-90% decreased in risk (Telinde et al)

Child bearing: Woman who has a live born child have a 20-50% decreases in risk. This reduction in risk increases with number of children born. However the protection offered by child birth is only temporary because the risk increases as time for her most recent child birth increases (Telinde et al)

Exogenous hormones: Exogenous estrogen especially that unopposed with progestins show an increase in the risk (Telinle et al)

Family history: Positive family history increases the risk by upto 3.5 fold (Telinle et al)

Race: There is 9 fold increases in incidence of leomyoma among black woman (North American clinics)

Diet and other factors: Obesity increases the risk of developing fibroids, while cigaritte smoking is associated with reduced risk (Parassiini F et al 1988). Myoma is associated with beef consumption where as high intake of green vegetable seems to have a protective effect (chiaffasino F etal 1999). Low physical activity, high mental stress were the risk factors in the etiology and pathogenesis of this disease (T.Katredry et al 1993)

ETIOLOGY

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

1. Myoma of Uterus.

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

It is suspected that hormone especially estrogen, growth hormones and progesterone play a role in the development and maintenance of uterus leiomyoma. Faber et al in 1972 and later Tamaya et al in 1978 in their study found that the smooth muscle cells including those of levels are sometime increased in woman with leiomyoma. Muram et al in 1980 found that evidence of hormonal dependence includes the increased frequency of leiomyoma after menarche and growth of leiomyoma during pregnancy.

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)

with in the uterus tumors can be

1. Intramural-75%
2. Subserous-10%
3. Submucous-15% (Shaw et al)

CLINICAL FEATURES (Telinde et al)

Abnormal menstruation

One third (30%) of patient with symptoms 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

There is second most common way of presentation. These symptoms are due to the pressure effect of the leiomyoma on the surrounding structures. They may be in the form of frequency or difficulty in micturition, constipation, low back ache or pain or discomfort in the lower abdomen. Importantly 30% of the patients come to us with complaints of pain.

MASS ABDOMEN

A few of the patient may present with complaints of only mass abdomen.

REPRODUCTIVE FAILURE

It must be remembered that infertility or recurrent pregnancy loss when fibroids are the sole implicated cause but is rare (5%)

Symptoms produced by leiomyomas are dependent on the location of the tumor with in uterus

Location	menstrual	pain	integrity	bulk
Intracavitary	+	+	+	-
Submucous	+	+	+	-
Intramural	+	+	+	-
Subserous	-	+	-	+
Pedunculated	-	+	-	+

LEIOMYOMA-VARIANTS (Stanley Robboy et al)

Ceullar leiomyoma

Haemorrhagic Cellular leiomyoma

Epithelid leiomyoma

(plexiform, leiomyoblastoma, clear cell)

Symplastic leiomyoma

Myxoid leiomyoma

Leiomyoma with hetero logous element

Leiomyoma unusual growth pattern

Diffuse leiomyomatosis

Intra vascular leiomyoma

Benign leiomyoma

Differentiated peritoneal leiomyoma

GROSS

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

MICROSCOPIC FEATURES (Robboy et al)

Leiomyoma is composed of interlacing fasicles of smooth muscle cells. The smooth muscle cells are markedly elongated and have eosinophilic cytoplasm and elongated cigar shaped muscle. In an uncompleted cases, it's nuclei are uniform and mitotic figures absent or sparse. Abdundant reticulin is present.

DEGENERATIVE CHANGES

Punnonem in 1965 and Arjoon in 1970, in their studies found that most forms of degenerations are the result of replacement of muscle

fibres by hyaline, collagen, blood, calcium, mucopolysaccharide or combination of these.

In 1964 Gupthaand hunter in their study found that cells admixed with smooth muscle cells in leiomyoma. Christopher et al in 1972 reported cellular leiomyoma to be more common in older woman with uterine atrophy. In the same study they also reported on symplastic leiomyomas. These are benign smooth muscle tumor of uterus which conatin large bizarre cells with large nucles. Mitotic count is less than 2/10 Hpf. Willamson E.O and Christopherson in 1972 reported that leiomyoma arising near serosa especially with pedicle may on rare occasions take up blood supply from the near by organs and detached them selves. These are called as parasitic leiomyomas

In 1977, Gasser and young in their studies reported neurilemmoma like leiomyoma. Leiomyoma some time resembles neurilemmoma due to stromal hyalinization. They usually demonstrate smooth muscle differentiation ultra strutually Mazur and Kraus in 1980 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).

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

Discovering of calcified uterine myomas is not frequent. Three case of uterine myoma reported as cause of pelvic classification and to establish differential diagnosis with bladder stones. Diagnosis is made by radiological studies in postmenopausal female patients (Hermida Perez et al 2003)

UTERINE PROLAPSE AND LEIOMYOMA

In Mittak Y et al study 2004 investigated the frequency and implications of incidental findings in uteri removed for prolapse. They found a high frequency of incidental findings that was greater than previously reported.

ADENOMYOSIS

Adenomyosis of the uterus is a condition characterized by a benign invasion of the endometrium in to the uterine musculature, associated with diffuse overgrowth of uterus (Jeffcoat et al). Adenomyosis is found in 25 to 40 % of all hysterectomy specimens by bird and associates indicate that it sufficient sections are obtained ectopic endometrium may be noted nearly 62% uteri removed for all causes (Bird C et al 1972).

In adenomyosis the uterus may be slightly or markedly enlarged, though the increase in size never reaches the large proportions seen so often with myoma. 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 (Jeffcoat et al).

Adenomyosis results grossly in an enlarged and globus uterus because of the myometrial hypertrophy that regularly accompanies it (Emge LA et al 1962).

The diagnosis may be suspected on cut section in the presence of depressed small cystic lesion in obivious but illdefined bulging zone

of muscle hypertrophy (Ackerman et al 2004). The cause of endometrial and muscle growth is the estrogenic hormone of the ovary lend support to the belief that adenomyosis will be found to be seen to an endocrine dysfunction of the ovary (Cullen et al 1908, Marcus et al 1961)

LEIOMYOMA UTERUS AND ASSOCIATED CONDITIONS

LEIOMYOMA UTERUS CORRELATION WITH CYCLICAL CHANGES ENDOMENTRIUM

In the presence of leiomyoma, the endometrium undergoes primarily histophysiological and age-related changes (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 (J.clin path). The myometrial tumor is large the over lying endometrium may be thinned out (CH-Bukley et al 1989).

LEIOMYOMA AND ENDOMETRIAL HYPERPLASIA

According to Block et al (1961) reported that 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 role in the synthesis of oestrogens.

Hyperplasia is the most common change in the endometrium associated with fibroid uterus. Mechanical cause may play a role (Acta Obs. Gynae. 1963).

Teleman S et al (2003) study of 390 specimens of hysrectomy, 316 cases presented different degrees of endometrial hyperplasias associated with leiomyoma. Leiomyoma and endometrial hyperplasia develop is a hormonal context. The most frequent type is simple hyperplasia suggesting a rare progression to highest grades and a possible protective role of leiomyoma as target tissue which capture estrogens.

The authors analysed 600 patients with uterine leiomyoma from hysterectomy performed for condition when leiomyoma were also studied for control purpose. Major conditions found include endomentrial hyperplasia. (Szajnbok et al 1990)

Biopsy specimens of the endometricm obtained from the 154 cases diagnosed showed that functional uterine bleeding has the higher incidence followed by myoma of the uterus. (Tsuka et al 1983)

Endometrium in association with myoma show little or no departure from the normal and the histologic sequence of cyclic change 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 (Novack et al).

Hyperplasia of the endometrium was recordable primary from patient with menopausal ovarian dysfunction in pt. with uterine myoma (Lond et al, 1982).

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

LEIOMYOMA AND ADENOMYOSIS

In Ben Aissia N et al study of analysis of 35 cases of adenomyosis, uterine fibroma is associated in 62% of cases (tunis med.2001)

Adenomyosis is more frequently associated with leiomyoma but essential adenomyosis was diagnosed most constantly when uterine enlargement was noted during menstrul period. (Thomas TS Jr et al 1989).

Adenomyosis was noted in 16% of 2,616 consequtive hystrectomy specimens examined during 7 year period. Multi parous women between the ages 30 and 50 years were most commonly affected. Abnormal uterine bleeding was the common symptom. Myohyperplasia, leiomyoma were usual 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 leiomyo

MATERIALS AND METHODS

SOURCE OF DATA

A total of 1680 hysterectomy specimens were received for various diseases in the department of pathology, Stanley Medical College from obstetrics and gynaecology department, RSRM, Chennai, from August 2003 to February 2006. Among the hysterectomy specimen received during the study period, only those specimens with fibroid were taken up for the study.

METHOD OF COLLECTION OF DATA

The material includes 375 cases of hysterectomy specimens along with fibroid with unilateral or bilateral salphingoophorectomy. The clinical details including LMP, LCB, cycle periodicity of the patients were taken from the records in medical records department.10% buffered formalin has been used for fixation of specimens. The following parameters size of the uterus, ovary, tubes, thickness of endometrium, number, site, size, shape and consistency of fibroids were noted.

Multiple bits of full thickness endometrium along with bits of fibroid of 2 to 3 cms were taken. A total of 465 hysterectomy specimens with fibroid were taken, among them 90 specimens showed complete obliteration of endometrium, so these specimens were not included in the study. The tissue slices were processed in various grades of alcohol and xylol. Paraffin blocks were prepared subsequently. Multiple thin sections of 5 microns were cut from the paraffin blocks and stained with routine method (Haematoxylin and eosin).

The endometrial changes of endometrium in relation to LMP. The results were tabulated

Photographs of the appropriate specimens and photomicrographs of the slides are furnished.

OBSERVATIONS AND RESULTS

INCIDENCE OF UTERINE LEIOMYOMA

1680 hysterectomy specimens were received during the period of August 2003 to February 2006 out of which 465 showed leiomyomas.

Incidence of leiomyoma among the hysterectomy specimen was 27.67%. (Table 1, Diagram 1)

AGE INCIDENCE OF LEIOMYOMA

The age group were divided as 1 to 9, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69 and above 69 years. Of these the age group 30 to 49 formed the largest. The mean age was 40 years. The youngest and oldest age incidence of leiomyoma were 30 and 62 respectively.

(Table 2, Diagram 2 & 3)

DISTRIBUTION ACCORDING TO SITE

Of 375 cases, 24% of fibroids were submucous in location. Intramural and subserous were 47.2% and 4.87% respectively. Both submucous and intramural locations of leiomyomas were 13.82%. Submucus and intramural were 4%. Submucous+subserous were 4.87%. The leiomyomas located in all three locations were only 1.6%. (Table 3, Diagram 4)

NUMBER OF FIBROID

Table 4, Diagram 5 show distribution of leiomyomas according to number.

216 had a single fibroid (57.6%) and 60 had two fibroids (16%)

Those with multiple fibroids were 99 (26.4%)

In this study most of the specimens had single fibroid.

CHANGES IN ENDOMETRIUM

Out of 375 specimens, 93 showed simple hyperplasia with an incidence of 24.8%, 0.8% showed complex hyperplasia, 0.8% were showed senile cystic hyperplasia. Irregular proliferative phase presented in 5.6%. The incidence of proliferative phase was 45.60%. Early secretory phase was 2.4%, late secretory phase was 13.6%. Atrophic endometrium was seen in 6.4% cases. (Table 5, Diagram 6)

CHANGES OF ENDOMETRIUM IN SUMUCOUS LEIOMYOMA

Out of 90 cases of submucous fibroid, the incidence of simple hyperplasia was 26.66%, proliferative phase was 40%, simple cystic hyperplasia was 3.33%. Irregular proliferative showed in 10% of

cases. Early secretory phase, late secretory phase, atrophic endometrium were 3.33%, 13.33% 3.33% respectively.

IN THE CASES OF INTRA MURAL LEIOMYOMA

Out of 177 cases of intramural fibroid, the incidence of simple hyperplasia was 20.33%. Complex hyperplasia was 1.69%. 1.69 cases showed irregular proliferation. The incidence of proliferative phase was 52.54% and early secretory phase, late secretory phase, atrophic endometrium were 1.69%, 11.86%, 10.16% respectively.

IN THE CASES OF SUBSEROUS FIBROID

Out of 18 cases of subserous fibroid, the incidence of proliferative phase and atrophic endometrium were 83.33% and 16.66% respectively.

The endometrial changes associated with fibroid on the basis of location were depicted in table 6.

AGE RELATED CHANGES IN ENDOMETRIUM WITH FIBROID

No cases were seen below 30 years

Between 30 to 39 years

168 cases were belonged to this age group. 23.2% showed simple hyperplasia. 53.6% of cases showed proliferative phase. Late secretory phase showed 12.5% of cases. 5.3% showed irregular proliferation. 3.6% showed early secretory phase. Atrophic endometrium showed only 1.8%.

Between 40 to 49 years

174 cases were in this age group.

The incidence of simple hyperplasia in this age group was 27.5%. 1.7% showed complex hyperplasia. 6.9% showed irregular proliferation. 1.7% showed early secretory phase. Proliferative phase, Late secretory phase and atrophic endometrium were 43.10%, 15.5%, 3.4% respectively.

Between 50 to 59 years

27 cases were reported in this age group. 22.2% showed simple hyperplasia. 22.2% showed proliferative phase. 11.1% showed senile

cystic hyperplasia. 33.3% showed atrophic endometrium. 11.1% showed senile cystic hyperplasia.

Between 60 to 69 years

There were only 6 cases seen in this category, showed atrophic endometrium (100%).

Above 69 years

No cases were seen in this age group. (Table 7)

ENDOMETRIAL CHAGES WITH FIBROID RELATED WITH LMP

In this study LMP in days were divided into 3 groups as 7 to 15, 16 to 30 and more than 30. (Table 8)

7 to 15 days

Only 15 cases belonged to this group

6 cases showed simple hyperplasia of incidence 40%

6 cases showed proliferative phase of incidence 40%

Only 3 cases showed Irregular proliferation (20%)

16 to 30 days

No. of cases belonged to this group was 171

42 cases showed simple hyperplasia (24.6%)

9 cases showed irregular proliferation (5.2%)

72 cases showed proliferative phase of incidence (42.1%)

39 cases showed late secretory phase (22.8%)

9 cases showed early secretory phase (5.3%)

Above 30 days

Total no. of cases in this group were 189

93 cases showed proliferative phase (49.2%)

45 cases showed simple hyperplasia (23.8%)

24 cases showed atrophic endometrium (12.6%)

3 cases showed complex hyperplasia (1.6%)

3 cases showed senile cystic hyperplasia (1.6%)

9 cases showed irregular proliferation (4.8%)

12 cases showed late secretory phase (6.3%)

ADENOMYOSIS ASSOCIATED FIBROID UTERUS

Of total 375 cases of fibroid study 108 cases showed adenomyosis accounting for 28.8%. (Table 9, Diagram 7)

Age Incidence

Table 10 and diagram 8 showed age incidence of adenomyosis associated with leiomyoma. No cases were found below 30 years.

33 cases out of 108 cases were in age group between 30 to 39 years (30.5%)

66 cases out of 108 cases were in age group between 40 to 49 years (61.1%)

9 cases out of 108 cases were in age group between 50 to 59 years (8.3%)

There were no cases seen above 59 years. (0.0%)

Maximum number of adenomyosis cases occurred between the age group 30 to 49 years. The incidence was 91.66%.

Based On LMP In Days

6 cases were in 7 to 15 days of LMP (5.55%)

48 cases were in 16 to 30 days (44%)

54 cases were in showed adenomyosis of LMP more than 30 days (50%) (Table 11, Diagram 9).

CHANGES IN ENDOMETRIAL THICKNESS

The normal endometrial thickness was 0.3 to 0.5cm . The reduced thickness was of range between 0.1 to 0.2cm. These reduced thickness were seen in endometrium of all submucous fibroids, large intramural fibroid and fibroid cases of all post menopausal women.

No association of leiomyoma with endometrial carcinoma was seen.

TABLE 1

INCIDENCE OF LEIOMYOMA

S.No.	*Disease*	No. of Hysterectormy specimens	Percentage
1	Fibroid	465	27.67%
2	DUB	270	16.07%
3	Ovarian Neoplasm	198	11.78%
4	Prolapse Uterus	630	37.5%
5	Cervical Dysplasia	48	2.8%
6	PID	36	2.14%
7	Adenomyosis	33	2.13%
	Total	**1680**	**100%**

TABLE 2

AGE INCIDENCE OF LEIOMYOMA

S.No.	Age in years	No. of cases	Percentage
1	1-9	-	-
2	10-19	-	-
3	20-29	-	-
4	30-39	168	44.8%
5	40-49	174	46.4%
6	50-59	27	7.2%
7	60-69	6	1.6%
7	70 & above	-	-
	Total	375	100

TABLE 3
LEIOMYOMA BASED ON LOCATION IN UTERUS

S.No.	Location	Number	Percentage
1	SubMucous	90	24%
2	Intra Mural	177	47.20%
3	Sub Serous	18	4.87%
4	Sub Mucous (+) Intra Mural	51	13.82%
5	Sub Serous (+) Intra Mural	15	4%
6	Sub Mucous + Sub Serous	18	4.87%
7	Sub Mucous + Sub Serous + Intra Mural	6	1.60%
	Total	375	100%

TABLE 4

LEIOMYOMA UTERUS BASED ON NUMBER

S.No.		Number	Percentage
1.	Single	216	57.6%
2.	Two	60	16%
3.	Multiple	99	26.4%
	Total	375	100%

TABLE 5

ENDOMETRIAL CHANGES ASSOCIATED WITH FIBROID UTERUS

S.No.	Endometrial Change	Number	Percentage
1	Simple Hyperplasia	93	24.8%
2	Complex Hyperplasia	3	0.8%
3	Senile Cystic Hyperplasia	3	0.8%
4	Irregular Proliferation	21	5.6%
5	Proliferative Phase	171	45.6%
6	Early Secretory Phase	9	2.4%
7	Late Secretory Phase	51	13.6%
8	Atrophic Endometrium	24	6.4%
	Total	375	100%

TABLE 6

ENDOMETRIAL CHANGES ASSOCIATED WITH FIBROID UTERUS ON THE BASIS OF LOCATION

S. No.	Changes in endometrium									Total
	Location of Fibroid	Simple Hyperp-lasia	Complex Hyperp-lasia	Senile Cystic Hyperp-lasia	Irregular Proliferative	Proliferative Phase	Early Secretory Phase	Late Secretory Phase	Atrophic Endometrium	
1	Sub Mucous	24 (26.6%)	-	3 (3.3%)	9 (10%)	36 (40%)	3 (3.3%)	12 (13.3%)	3 (3.3%)	90 (24.0%)
2	Intra Mural	36 (20.3%)	3 (1.7%)	-	3 (1.7%)	93 (52.5%)	3 (1.7%)	21 (11.9%)	18 (10.2%)	177 (47.2%)
3	Sub Serous	-	-	-	-	15 (83.3%)	-	-	3 (16.7%)	18 (4.8%)
4	Sub Mucous + Intra Mural	24 (47%)	-	-	3 (5.9%)	18 (35.3%)	3 (5.9%)	3 (5.9%)	-	51 (13.6%)
5	Intra Mural + Sub Serous	3 (20%)	-	-	3 (20%)	6 (40%)	-	3 (20%)	-	15 (4.0%)
6	Sub Mucous + Sub Serous	6 (33.3%)	-	-	-	3 (16.7%)	-	9 (50%)	-	18 (4.8%)

7	Sub Mucous + Sub serous + Intra Mural	-	-	-	3 (50%)	-	-	3 (50%)	-	6 (1.6 %)
Total										375 (100 %)

TABLE 7

AGE RELATED CHANGES IN ENDOMETRIUM WITH FIBROID

S. No	Age in years	Simple hyper p-lasia	Complex hyper p-lasia	Senile cystic Hyper p-lasia	Irregular Prolif era-tive	Prolif era-tive phase	Early secre-tory phase	Late secre-tory phase	Atrophic endo met-rium	Total
1	1-9	-	-	-	-	-	-	-	-	
2	10-19	-	-	-	-	-	-	-	-	
3	20-29	-	-	-	-	-	-	-	-	
4	30-39	39 (23.2 %)	-	-	9 (5.3%)	90 (53.6 %)	6 (3.6%)	21 (12.5 %)	3 (1.8%)	168 (44.8 %)
5	40-49	48 (27.6 %)	3 (1.7%)	-	12 (6.9%)	75 (43.1 %)	3 (1.8%)	27 (15.5 %)	6 (3.4%)	174 (46.4 %)
6	50-59	6 (22.2 %)	-	3 (11.1 %)	-	6 (22.2 %)	-	3 (11.1 %)	9 (33.3 %)	27 (7.2%)

7	60 -69	-	-	-	-	-	-	-	6 (100 %)	6 (1.6%)
8	70 and abov e	-	-	-	-	-	-	-	-	
										375 (100 %)

TABLE 8

ENDOMETRIAL CHANGES IN FIBROID BASED ON LMP

S. No	LMP in days	Simple hyper p-lasia	Complex hyper p-lasia	Senile cystic Hyperplasia	Irregular Prolifer a-tive	Prolif era-tive phase	Early secre-tory phase	Late secre-tory phase	Atrophic endo metrium	Total
1	7-15	6 (40%)	-	-	3 (20%)	6 (40%)	-	-	-	15 (4.0%)
2	16-30	42 (24.5 %)	-	-	9 (5.2%)	72 (42.1 %)	9 (5.2%)	39 (22.8 %)		171 (45.6 %)
3	>30	45 (23.8 %)	3 (1.6%)	3 (1.6 %)	9 (4.8%)	93 (49.2 %)	-	12 (6.3%)	24 (12.7 %)	189 (50.4 %)
									Total	375 (100 %)

TABLE 9
INCIDENCE OF ADENOMYOSIS

No.	Percentage
108	28.8%

TABLE 10
OCCURRENCE OF ADENOMYOSIS ASSOCIATED WITH FIBROID
UTERUS AGE RELATED

S.No.	Age in years	Adenomyosis	Percentage
1	1-9	-	-
2	10-19	-	-
3	20-29	-	-
4	30-39	33	30.55%
5	40-49	66	61.11%
6	50-59	9	8.33%
	60-69	-	-
7	70 & above	-	-
	Total	108	100%

TABLE 11
ADENOMYOSIS ASSOCIATED WITH FIBROID UTERUS
BASED ON LMP

S.NO.	LMP in days	Adenomyosis	Percentage
1	7-15	6	5.55%
2	16-30	48	44.44%
3	>30	54	50%
	Total	108	100%

DISCUSSION

Leiomyoma of the uterus is an extremely common neoplasm. Many of these tumours are small and so undetected and are often incidental findings. In the current study over a period of 2.5 years (August 2003 to February 2006), 1680 hysterectomy specimen were received of which 465 revealed leiomyomas with an incidence of 27.67%. Ackerman et al did a meticulous study of 100 consecutive hysterectomy specimen of which 77 revealed leiomyomas. The low incidence in our study can be partly explained by conservative management of leiomyoma by gynaecologists.

Although Ackerman et al reported 84% of leiomyomas as multicentric, current study showed an increased incidence of single fibroids. Of 375 leiomyomas 52% were single and 20%, 28% were double and multiple respectively. This difference needs to be further evaluated.

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 menopausual women (Cabrera et al 1994). In current study of 375 cases, 342 cases were in the age group between 30 to 49 years (91.2%). The mean age was 40 years. In this study most of the cases occurred in premenopausal women. Only 3.2% of cases were seen in post menopausual women age group. This could be explained of the theory of enhanced estrogen stimulation causing uterine fibroids is concerned. (Muram et al).

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 of 375 cases 47.2% of cases showed intra mural fibroids. 24% showed in submucous region only 4.87% were subserous location. Both in submucous and intramural region were 13.82%. This finding is in accordance with the reference cited.

ENDOMETRIAL CHANGES

In the current study of 375 cases, 45.6% showed proliferative phase and 6.4% showed atrophic endometrium. The early and late secretory phase were seen in 2.4% and 13.6% respectively. 5.6%

showed irregular proliferation. These features were in accordance with number of literature studied. 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, however the changes are insufficient to warrant a diagnosis of hyperplasia but are recognizable as those of a prolonged proliferative phase in some patients. Mitotic activity continues beyond the 14^{th} day of the cycle.

According to Zhleznov BI et al., 1990, in the cases of leiomyoma, the endometrium undergoes primarily histopathological and age related changes According to Land echowskij JD et al., 1982,. endometrial structures were normal in 54% of 178 myoma patient and phases of incomplete secretion were recorded from 14.6%

If the myometrial tumour is large, the overlying endometrium may be thinned out (CH Bukley et al 1989). The atrophic endometrium were the most constant morphological changes in the presence of leiomyoma mainly of submucous type (83%). Atrophy is not only due to mechanical pressure but also from the post menopusual hormonal insufficiency (L.Deligdish et al Study- J. clinic Path 1970). In accordance with this study, the current study showed thinned out

endometrium of 0.1 to 0.2cm in all the 90 submucous fibroid cases and in 57 out of 177 cases of intra mural fibroid and 24 cases of post menopausual women.

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 specimen, 316 cases presented with different degrees of endometrial hyperplasia with leiomyoma. Leiomyoma and endometrial hyperplasia develop in hormonl context. The most frequent type is simple hyperplasia, suggesting a rare progression to highest grades and a possible protective role of leiomyoma as a target tissue which capture estrogen (Teleman S et al, 2003). Lattinen (1964) reported that hyperplasia was the most common change in the endometrium belonging to myoma uterus (J clin path 1970). In accordance with these studies the current study showed 93 cases of simple hyperplasia out of 375 cases. The incidence was 24.8%. Complex hyperplasia, senile cystic hyperplasia of incidence of 0.8% of each. These features are due to protective role of uterine myoma.

Although Deligdish et al study of submucous myoma of 30 cases in the age group between 31 to 52 years showed glandular atrophy over myoma was the constant finding and margin of myoma showed frequently of hyperplastic glands, in the current study out of 90 cases of submucous leiomyoma the incidence of simple hyperplasia was 26.66%. 40% showed proliferative phase and only 3.33% showed atrophic endometrium. This could be attributed to the young age of the patient involved (i.e. active reproductive age group). (Malcom. C, Anbderson et al).

In the presence of leiomyoma the endometrium undergoes primarily histophysiological and age related changes (Zhelezenov Bi et al 1990). Hyperplasia of the endometrium was recordable primarily from the patient with menopausal ovarian disfunction (Zentrabl gynekol 1982). In the current study most of the cases were between 30 to 49 years. Of this group simple hyperplasia was seen in 25.4%. 48.2% showed proliferative phase. 14% showed late secretory phase. Only 9 cases belonged to age more than 55 years. Of these 6 cases showed atrophic endometrium and 3 cases showed senile cystic hyperplasia.

Goranjon et al 1961 found high estrogen levels in women with uterine fibroid and believed that the endometrium played role in the synthesis of estrogens. Novak and wood druff (1962) described the association between myoma and the non-ovulatory type of cycle with hyperplasia of endometrium. In some patient, however the changes are insufficient to warrant a diagnosis of hyperplasia but are recognizable as those of a prolonged proliferative phase. Mitotic activity continuous beyond the 14th day of cycle (CH Bukley et al). In this study out of 375 cases 171 cases had LMP of 16 to 30 days and 189 cases more than 30 days of LMP. 165 cases out of 375 cases showed persistent proliferative phase with LMP more than 15 days. 87 cases out of 375 cases showed Hyperplasia had LMP of more than 15 days. This showed unopposed estrogenic action (Hyper estrogenic stage). 24 cases showed atrophic endometrium, were postmenopausal women.

Adenomyosis in leiomyoma was associated feature seen in the study. 108 out of 375 leiomyomas was associated with adenomyosis forming 23.8%. Ben Aissia N et al (2001) had reported 62% and Raju GC et al (1980) reported 16% and Thomas JS et al (1989) had noted more frequent association. Raju GC et al study 1980, noted that association of adenomyosis in leiomyoma was most commonly

seen in multiparous women between the ages 30 and 50 years. The present study also, 91.66% of leiomyoma in the age group of 30 to 49 were seen to be associated with adenomyosis.

No endometrial and uterine malignancies were reported in this study. Site wise distribution of leiomyoma show persistent proliferative feature or simple hyperplasia, indicates hyperestrogenic status. But there were no abnormal incidence of more worrisome lesions like complex/atypical hyperplasia.

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. The present study also reveal there is no association of leiomyoma and endometrial carcinoma. This points to the fact, that there could be protective role of leiomyoma on endometrium hypothesized by Teleman S et al 2003.

SUMMARY AND CONCLUSION

During the study period between August 2003 to February 2006, 375 hysterectomy specimens with leiomyoma were taken up for studying endometrial changes

1. The incidence of leiomyoma was 27.67%
2. Most of leiomyoma were seen in premenopausal women, of age group between 30 to 49 years with an incidence of 91.2%
3. Only 3.2% of were seen in postmenopausal age group.
4. This study showed a higher incidence of unicentric fibroid with an incidence of 52%
5. Most of the fibroids were occurred in intramural location of an incidence 47.2% followed by submucous fibroid with an incidence of 24%
6. The endometrium were thinned out (0.1 to 0.2cm) in all the 90 submucous fibroid, 57 intramural fibroid and 24 of postmenopausal women
7. 45.6% showed proliferative phase. 6.4% showed atrophic endometrium.
8. 93 showed simple hyperplasia that is 24.8%. Complex hyperplasia and senile cystic hyperplasia were 0.8% each.

9. Of 90 submucous myoma, simple hyperplasia was seen in 26.66%. 40% showed proliferative phase and only 3.3% showed atrophic endometrium.
10. Most of the cases were between 30 to 49 years (91.2%). In this age group, simple hyperplasia seen in 23.4%. 44.4% showed proliferative phase. 12.8% showed late secretory phase.
11. Above 55 years age group only 9 cases were reported. Of these 6 showed atrophic endometrium and 3 showed senile cystic hyperplasia.
12. In this study, 171 cases had LMP of 16 to 30 days and 189 had more than 30 days of LMP.
13. 165 cases showed persistent proliferative phase with LMP more than 15 days.
14. 87 cases showed endometrial hyperplasia with LMP of more than 15 days.
15. Adenomyosis was associated with 108 cases with an incidence of 23.8%.
16. Maximum mumbers of Adenomyosis was seen between the age group 30 to 49 years. The incidence of adenomyosis in this age group was 91.66%.

The incidence of leiomyoma is almost equal to other data available in the world literature.

Endometrial changes noted also correlated with findings of other authors.

Many authors had worked on the endometrial changes in fibroid uterus. A comparison with those studies revealed then the current observations were corrobarative except for few variations.

A striking observation was the association of adenomyosis and fibroid, 23.8% 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 constituted 252 out of 375 cases, which means 67% showed hyperestrogenic status, which also explains the various menstural disturbance 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, here there were significant number of cases showed proliferative phase, which could only be explained by the lower age group affected.

No association of leiomyoma with endometrial carcinoma was seen. There were very few cases reported in the literature which substantiates the hypothesis of protective role of leiomyoma.

Diagram 1

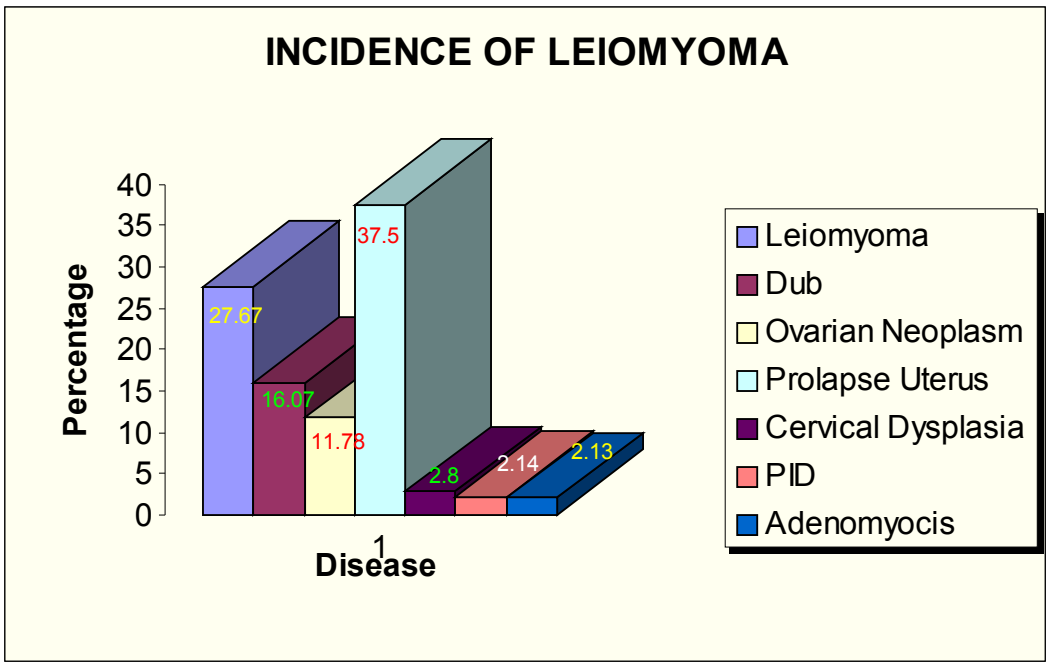


Diagram 2

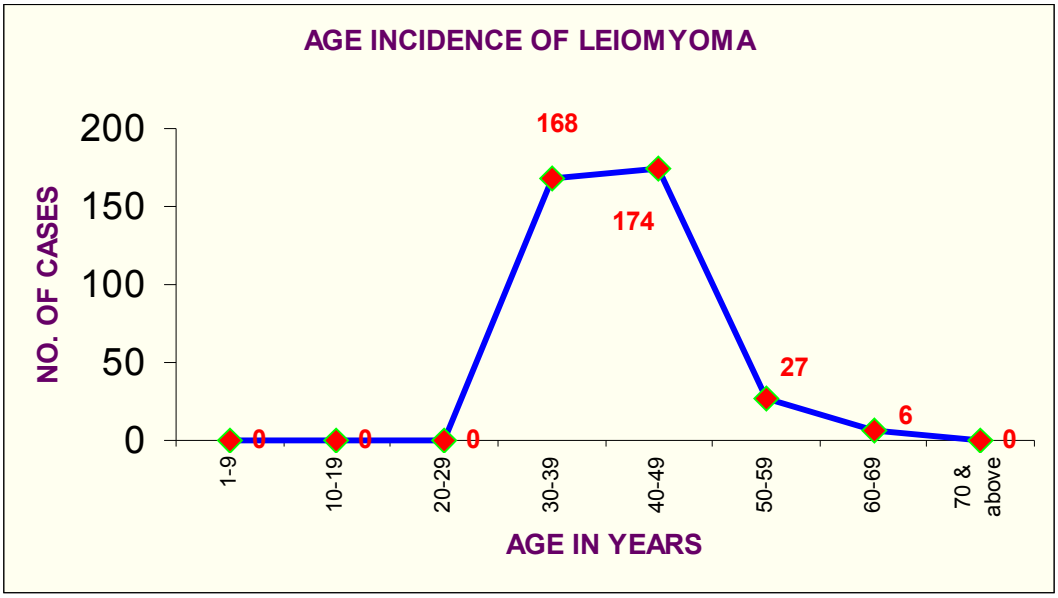


Diagram 3

AGE INCIDENCE OF LEIOMYOMA

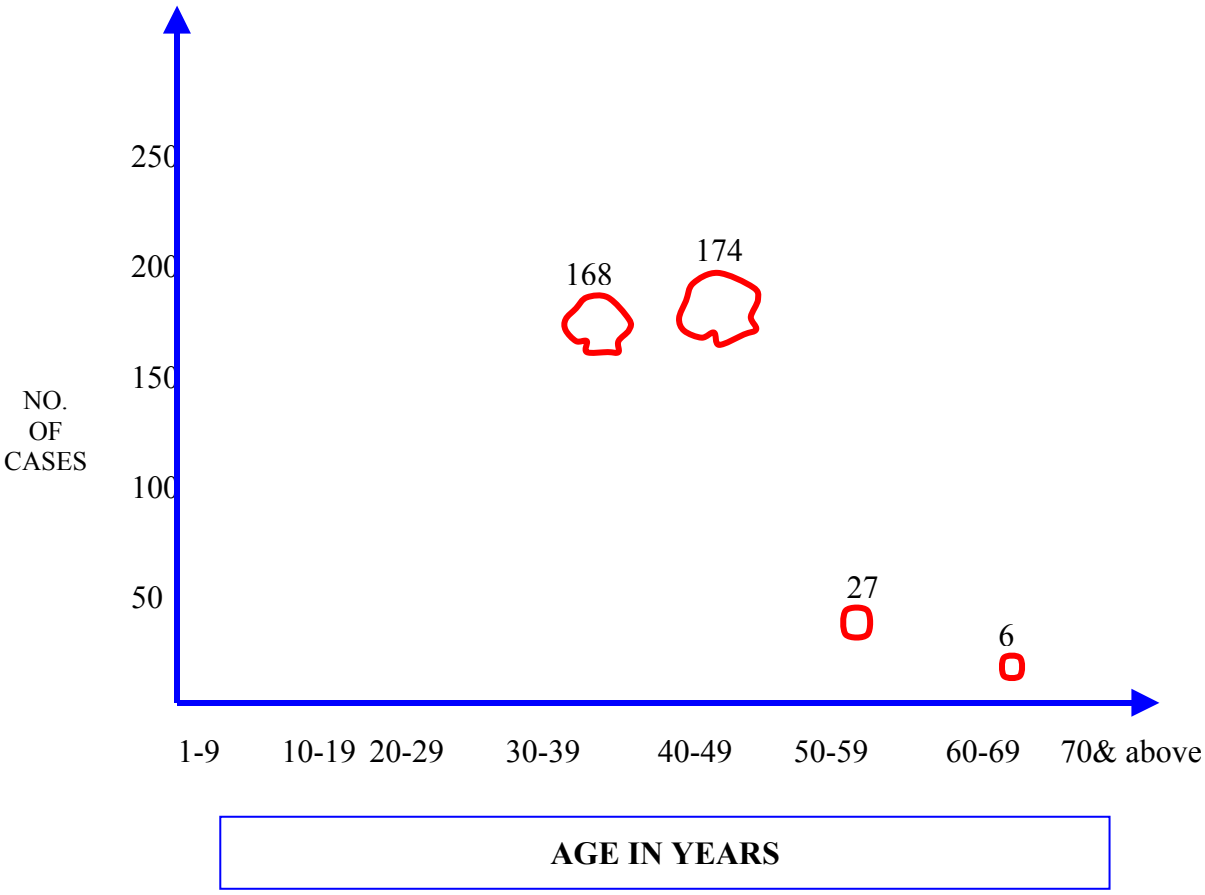
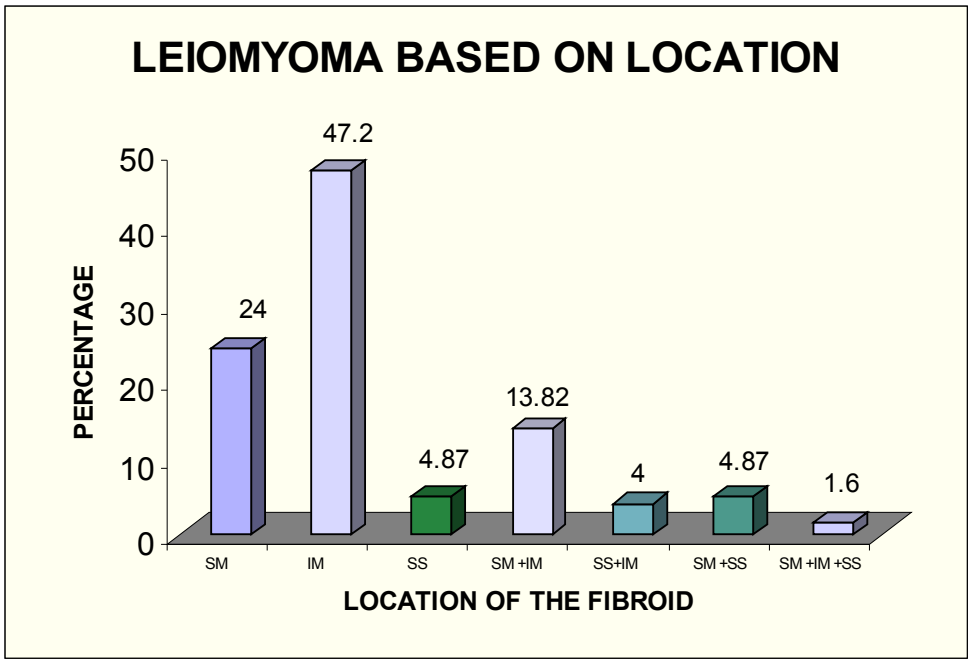


Diagram 4



SM-Submucous, IM-IntraMural, SS-Subserous

Diagram 5

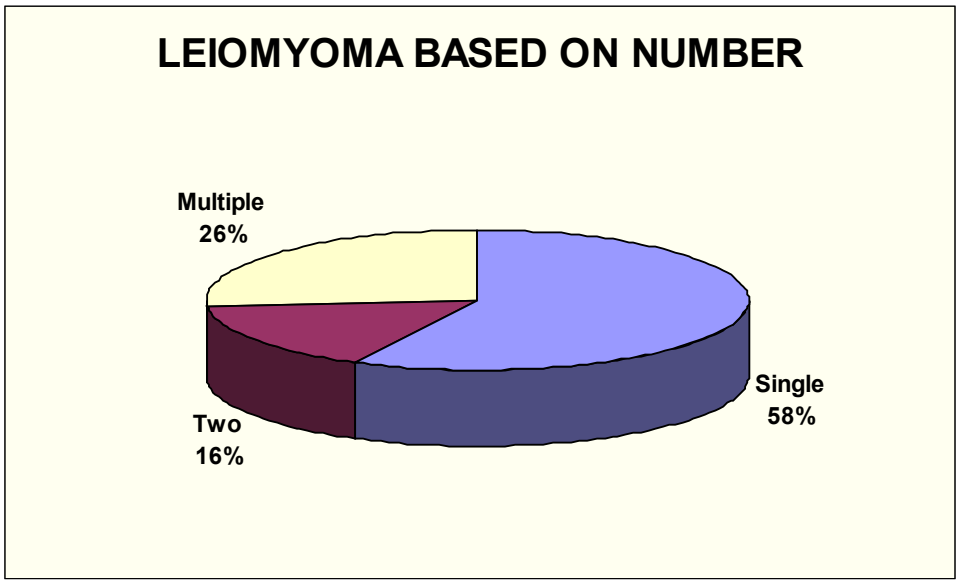


Diagram 6

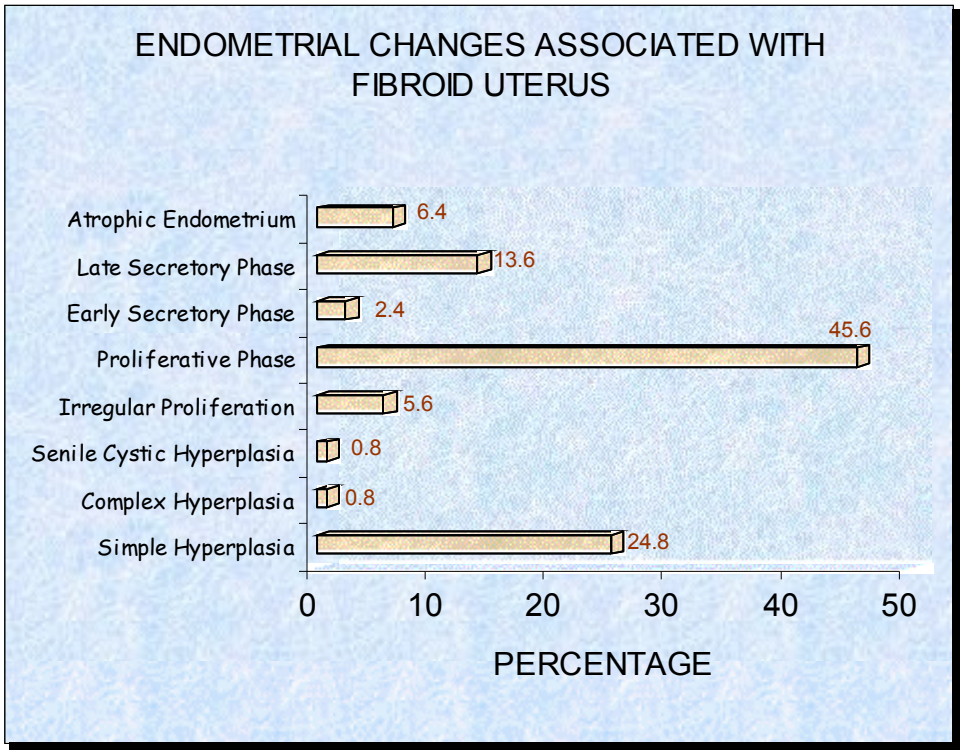


Diagram 7

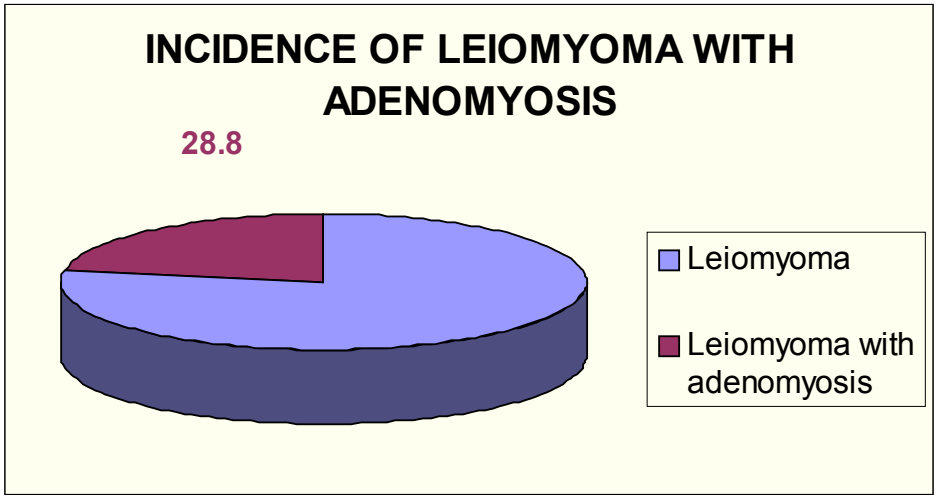


Diagram 8

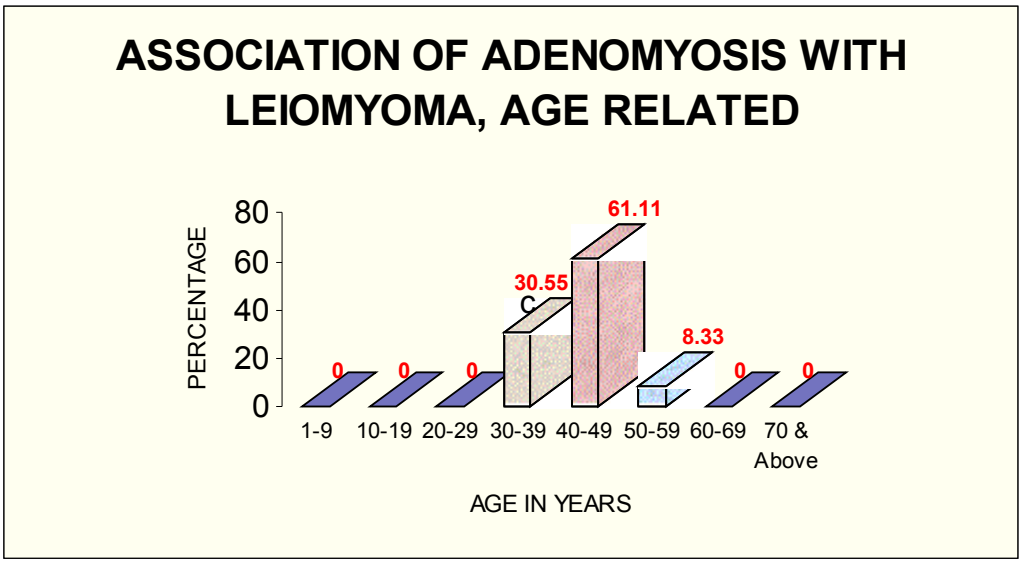
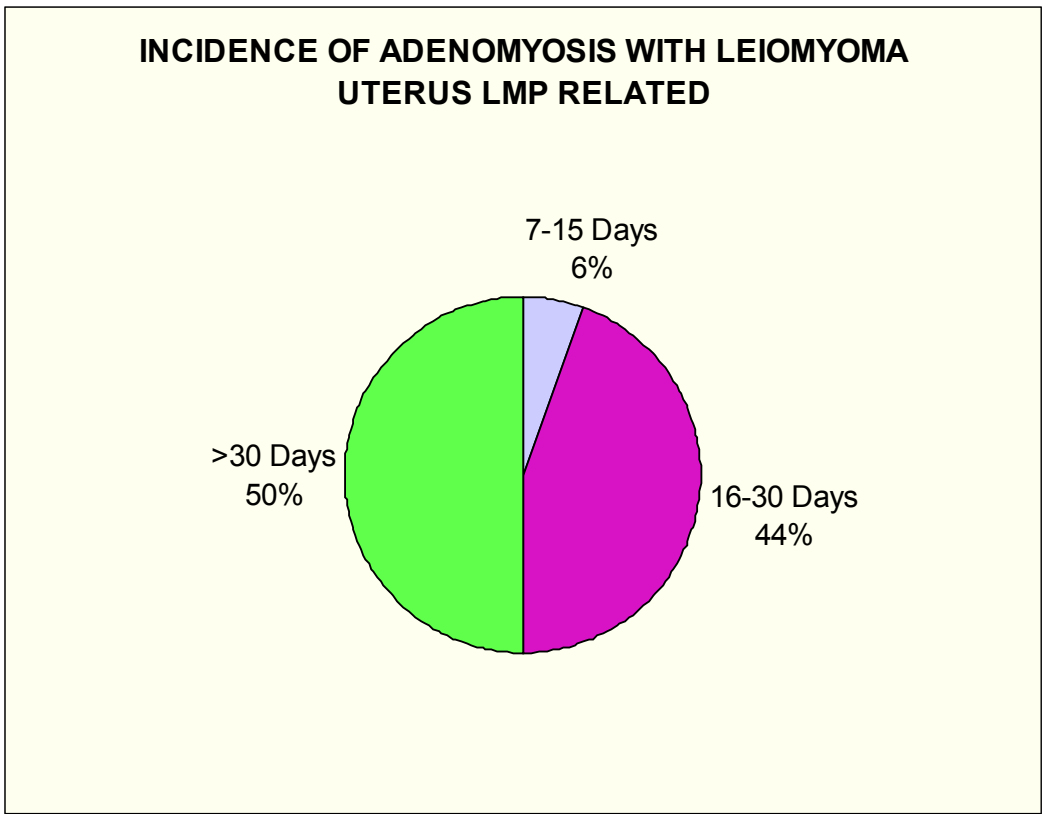


Diagram 9



PROFORMA

Name:

Age:

I.P. No.

Unit:

Address:

Hospital

Diagnosis:

Date of Admission:

Date of Discharge:

Complaints

1) Menstrual:

a) Menorrhagia:
b) Polymennorhoea:
c) Metrorrhagia
d) Oligomennorhoea:
e) Hypomennorhoea:
f) Amennorhoea:
g) Normal Periods:

2) Bulk symptoms:

a) Frequency of micturition:
b) Difficulty in micturition:
c) Difficulty in defecation:
d) Low back ache:

3) Pain

a) Lower abdominal pain:
b) Dysmennorhoea:
c) Low back ache:

4) Dyspareunia:

5) Mass abdomen:

6) White discharge:

7) Fever:

Menstrual History:

Menarche: Present Periods:
Previous Periods: LMP:

Obstetric History:

Married Since: H/0. MTP:
NOC: Contraception:
NOC alive: Sterilized or not:
Mode of deliveries: Others:
LCB:

Past History:

H/0 similar complaints in past:

Treatment underwent if any:

H/0. PID:

H/o. previous myomectomy:

Personal History:

Fertility:

Menstrual function:

Family History:

H/o. similar disease
H/o. Gynaec Ca
H/o. Breast Ca

Examination:

Built: Surface:
Nourishment: Mobility:
Ht:

Wt:
Anemia:
Others:
Pulse:
BP:

S/E: Cervix:
Upwards:
Midposition:
Downwards:

P/A

Scar:
Mass:

Size of Mass:
Tenderness:
Consistency:
Borders:

P/V

Uterus
Anteverted:

Midposition:
Retroverted:
Size:
Fornices:

Provisional Diagnosis:
Investigations:

Hb:
RBC:
PCV:
BT & CT:
Blood Urea:
S. Creatinine:
USG/CT: No.

Site:
Size:
Ut. Vol:

Endometrial Biopsy:

BIBLIOGRAPHY

1 Ackermann – text book of surgical pathology, page – (1577-1578)

2 A Clinico pathological study of the relationship between adenomyosis and other hormone dependent uterine lesion

3 Ackermans, Cramer SF, Paterl A. The frequency of uterine leiomyomas. AmJ Clinical Pathology 1990:94 435-438.

4 Acta Obstet Gynac. Second 42. 383-398 (1963)

5 Arjoon PD. Uterine leiomyoma; incidence of degenerative change and a correlation of associated symptoms. Obstet Gynacol 1970;432-436.

6 Ascheim S. and Zondek E. and Hormon (1927). Klinische woehenschrift, 6, 1322.

7 Augensen K. Case report; Uterine myoma in a 15 year old girl Acta Obstetrica of Gynaecologica Scandimavia 1818; 60:591

8 Barber H.R.K. and Graber E.A., Gynaecological tumors in Childhood and adolescence obstet Gynecol. Surv. 28:357, 1973.

9 Bayard F. Damilano S. Robel P. Baulieu EE (1978) Cytoplasmic and nuclear estradiol and progesterone receptors in human endometrium. J Clin Endocrinol Metab 46: 635.

10 Ben Aissia N, Berriri H, Gara F. Tunis Med 2001. Aug Sep; 79(8-9); 447-51.

11 Birel C.C., Mc Elin, T.W., and Manalo. Estrella P. The elusive adnomyosis of the uterus revisited Am J Obstet Gynecol, 112:583, 1972.

12 Block F (1961) die pathologic der uterusmyomearch gynace 195-166-177, J-Cline path. 1970

13 Bolck F(1961) Die Pathologic Der Uterusmyome Arch Gynome 195-166-177. J-Chine Path-1970.

14 Borell U. Fernstro, I, Westman A (1953) Hormonal influence on the uterine arteries. Acta Obstet Gynecol Scand 38:364.

15 Bulmer J N, Hollings, D, Ritson A 1987 Immunocytochemical evidence that endometrial stromal granulocytes are granulated lymphocytes. Jornal of Pathology 153: 281-287.

16 C.H. Bukley (1989). H-Fox Biopsy Pathology of Endometrium

17 Cabera J, Muceintes F, Klassen R, Acosta S, Oliva JP Departments de Obstetricia of Ginecologia, Universidad de conception Rev. Chil Obstet Ginecol. 1994; 59(1): 39-43 Related articles links

18 Cabrerce J et al Rev chil obstet Gine Col 1994: 59(1) 39-43

19 Christopherson WM, William EO, Gray LA. Leiomyosarcoma of the uterus cancer 1972;29;1512.

20 Clyman MJ. Spiegelman I Ross T (1982) Appearance of ronofilaments and absence of microtubules in human endometrial glandular

epithelium. Diagen Gynecol Obstet 4: 173.

21 Cooke I D, Morgan C A, Parry T E 1972 Correlation of endometrial biopsy and plasma progesterone levels in infertile women. Journal of Obstetrics and Guynaecology of the British Commonwealth 79: 647-650.

22 Cullen, T.S: Adenomyoma of uterus. Philadelphia, W.B. Saunders Company, 1908

23 Dallenbach F D, Dallenbach-Hellweg G (1964) Immunohistologische Untersuchungen zur lokalisation des Relaxins in menschlicher Plazenta und Dezidua. Virchows Archiv fur pathologischen Anatomie und Physiologie und fur klinische Medizin 337: 301-316.

24 Dallenbach FD. Dallenbach-Hellweg G (1968) Fluoreszenzmikroskopische Tagesdiagnostik des menstruellen Zyklyus and erste Anzeichen der senilen Involution Verh Dtsch Ges Pathol 52:342.

25 Dallenbach-Hellweg G (1981) Histopathology of the endometrium Springer Verlag, Berlin, pp 26-31.

26 Davidson EH (1965) Hormones and genes. Sci Am 212:36

27 Dubrauszky V, Pohlmann G (1960) Strukturveranderungen am Nukeolus von Korpusen dometriumzellen wahrend der Sekretionsphase Naturwissenschaften 47:523.

28 Dupantier N, Finan MA, Barbet. J-Repord Med 2003 Jan 48(1):23-7.

29 Edwards R. Brush MG. Taylor RW (1969) The uptake and intracellular distribution of (1.23H) progesterone by human endometrium. J Endocrinol 45/1: III-IV

30 Emge LA., Problems in the diagnosis of adenomyosis uteri. West J. surg, 64:291, 1956.

31 Faber M, Conrad S, Heinrichs WL, Herrman WL. Estradiol binding by fibroid tumors and normal myometrium. Obstetrics and Gynaecology of British Common Wealth 1972:77; 976-975

32 Fasske E, Morgenroth K. Themann H, Verhagen A (1965) Vergleichende elektronenmikroskopische Unbtersuchungen von Proliferationsphase. Glandular-cystischer Hyperplasie und Adenocarcinom der Schleimhaut des Corpus uteri. Arch Gynakol 200:473

33 Feldhaus FJ, Themann H, Wagner H, Verhagen A (1977) Feinstrukturelle Untersuchungen uber das Nuclear-Channel-System im menschlichen Endometrium. Arch Gynakol 223:195

34 Ferenczy A (1994). Anatomy and histology of uterine corpus. In Blaustein's Pathology of Female genital tract. Kurman R.J. (edi) 4th edition, New York, springer – verleg.

35 Ferenczy A. (1980). Regeneration of human eadometrium. In progress in surgical pathology. Fennoglio C.M., Wolff M. (edi) Volume I, New York, Masson publishing.

36 Feyrter F, Froewis J (1949) Zur Frage der hellen Zellen in der Schleimhaut der menschlichen Gebarmutter. Gynaecologia (Basel) 127:33

37 Fox H, Buckley C H (1982) Pathological factors involved in infertility. In: Blaustein A (ed) Pathology of the female genital tract. Springer Verlag, New York, pp 828-837.

38 Gigon U, Herzer H, Stamm O, Zarro D (1970) Endometriumveranderungen und luteotrope Sekretionsanomalien bei Gelbkorperinsuffizienz. Zeitschrift fur Geburshilfe und Gynakologie 173: 304-323.

39 Gisser SD, Young I. Neurilemoma like uterine myoma. AmJ Obstet Gynacol 1977;129;389-392.

40 Gorski J, Gannon F (1976) Current models of steroid hormone action: a critique. Annu Rev Physiol 38:425

41 Granjon, Yanotti and Cedrad (1961). J. Clin Path. 1970, 23, 676-680.

42 Guillebaud J. and Bonner J. (1978) Longer though lighter menstrual and intermenstrual bleeding with copper as compared toinert intra uterine device. Br Jobstet aynecol 85, 707 -12

43 Hafez ESE. Ludwig H. Metzger H (1975) Human endometrial fluid kinetics as observed by scanning electron microscopy. Am J Obstet Gynecol 122:929

44 Hallberg L., Hoegdahl A., Nilsson L. and Rybog (1966). Mestrual blood loss – a population study. Acta obstet aynecol scand 45, 320 -51.

45 Hamperl H (1954) uber die endometrialen Granulozyten, Klinische Wochenschrift 32: 665-668.

46 Hermida Perez J, Vento Remedies T, Ramos Perez AV Guerro Abrante P - Arch ESP Urol-2003 Mar:56(2):165-9 calcified uterine myoma-presentation of 3 cases.

47 Hermida perez J, Vento Remedios T, Ramos Perez AV Guerro abrante P –Arch ESP Urol-2003 Mar:56(2):165-9 calcified uterine myoma-presentation of 3 Cases

48 Hitschmann F. Adler L (1908) Der Bau der Uterusschleimhaut des geschlechtsreifen Weibes mit besonderer Beruchsichtigung der Mestruation Monatsschr Geburtshitfe Gynakol 27:1

49 Hu J, Surti U. subgroups of uterine leiomyomas based on cytogenetic analysis. Human Pathology 1991:22:1009-1016

50 J Reprod Med. 1995 Aug: 40(8): 595-600. Related Articles, Links Epidemiology of Uterine Leiomyomas with an etiologic hypothesis Crammer SF, Horiszny JA, Leppert P.

51 Jeffcoat text book of Clinical Gynaecology; 260-289

52 Johannisson E, Nilsson L (1972) Scanning electron microscopy study of the human endometrium. Fertil Steril 23:613

53 Jones G S, Aksel S, Wentz A C (1974) Serum progesterone values in the luteal phase defects: effects of chorionic gonadotropin. Obstetrics and Gynecology 44: 26-34.

54 Kairi – vassi latou E, kontsgiamni-Eur. J. gynacol-oncol 2004-25(2) 222-4

55 Kairi-Vassi Latsu E, Kontogianni-Eur. J-Gynac-oncol 2004-25(2), 222-4. A Clinico pathological study of the relationship between adenomyosis and other hormone dependant uterine lesion.

56 Katzenellenbogen B S. (1980). Dynamics of steroid hormone receptor action, Annu Rev physiol 42:17

57 Kauppila A. Janne O. Stenback F. Vihko R (1982a) Cytosolic estrogen and progestin receptors in human endometrium from different regions of the uterus. Gynecol Oncol 14:225

58 Kauppila A. Kujanasuu E. Vihko R (1982b) Cytosol estrogen and progestin receptors in endometrial carcinoma of patients treated with surgery. Radiotherapy, and progestin in Cancer (Philad) 50:2157

59 Keller R (1911) Gefabveranderungen in der Uterussehleimhaut Zur Zeit der Mestruation z Geburtshilfe Gynakol 69:333

60 Kitawaki J, Obayastri H, Ishihara H, Koshiba H, Kusuki I, Kado N, Tsukamoa. K Hanje. H. Hum Reprod 2001 Jan; 16(1): 51-55.

61 Kustermann H (1930) Systematische histologische Untersuchungen uber die Venen des Uterus.Z Mikrosk Anat Forsch 20:417

62 L.Deligolish and M.Loewenthal J. Clin. Path., 1970, 23, 676-680. Endometrial changes associated with myoma of the uterus.

63 Laatikainen T, Andersson B, Korkkaimen J, Wohlstrom T (1983) Progestin receptor levels in endometria with delayed or incomplete secretory changes. Obstetrics and Gynecology 62: 592-598.

64 Lalitinen (1964), Lalitinen study of endometrial hyperplasia J.Clin path 1970, 23, 676-680.

65 Landechowskij JD, Al-Birawi AS, Kulikov LS. Zentrabl Gynakul. 1982; 104(13): 809-17. Characterization of the endometrium in patients with uterus myoma.

66 Malcom. C. Anderson, Stanley J Robboy, Peter Russel - Book of gynaecological Pathology (304-314)

67 Marcus C.C. Relationship of adenomyosis uteri to endometrial hyperplasia and endometrial adenocarcinoma Am J Obstet Gynecol; 82:408, 1961.

68 Markee J E (1950) The morphological and endocrine basis for menstrual bleeding. In: Meig J V, Sturgis S M (eds) Progress in gynecology. Stratton, New York, vol II.

69 Mazur MT, Kraus FT, Histogenesis of morphologic variations in the tumours of the uterine wall. Am J Surgical pathology 1980; 4;59-74.

70 McKay DG, Hertig AT. Bardawil W. Velardo JT (1956) Histochemical observations on the endometrium: I Normal

endometrium II. Abnormal endometrium. Obstet Gynecol 8:22, 140.

71 Meyer R: Die Pathologische Anatomic der Gebarmutter Henke Lubarsch Handbuch Der Spezie Pathologische Anatomie and Histologie. Bcl VII, Erster Theil. Berlin, Julius springer 1930.

72 Monch G (1918) Uber Rundzellenknotchen im Endometrium. Arch Gynakol 108:483

73 Moricard R (1954) Criteres morphologiques uterins et vaginauz de 1'exploration cytohormonale dans la phase luteate In: Colloques sur "La function luteale". Masson. Paris. P 185.

74 Moszkowski E, Woodruff J D, Jones G E S (1962). The inadequate luteal phase. American Journal of Obstetrics and Gynecology 83: 363-372.

75 Muram D, Gillieson M, Wallers. JH Myomas of the Uterus AmJ Obstet Gynacol 1980; 138; 16-19.

76 Novok et al, Novek text book of Gynaec Pathology

77 Obs and Gyn, Clinics of North America, 625-628

78 Obset Gynecol 1999 Sep:94(3): 395-8. Related Articles links Diet and Uterine myomas Chiaffarino F, Parazzini F, Ha Vecchia C, Chatenood L, Di Cintio E, Marisco S.

79 Parazzin F, La Vechia C, Negri E, Fedele of Balotta F. Epidemiologic Characteristics of Women with Uterine Fibroids Obstet Gynacol 1988; 72:853-857

80 Plotz J (1950) Der Wert der Basaltemperatur fur die Diagnose der Menstruationsstorungen. Arch Gynakol 177:521

81 Punnonen R. Necrosis of uterine myomata. Acta obstetrica et gynecologica Scandinavia 1965;4;502-505

82 Raju GC, Narayan singh V, Woo J, Jankey N Aust NZJ obstet Gynacol. 1988, Feb 28(1): 72-3.

83 Ramsey EM (1955) Vascular patterns in the endometrium and the placenta Angiology 6:321

84 Rev Med Chir Soc Med Nat Iasi 2003 Apr-Jun; 107(2): 379-82.

85 Ritson A, Bulmer J N (1987) Endometrial granulocytes in hyman deciduas react with a natural killer (NK) cell marker. Immunology 62: 329-331.

86 Ross M.H, Romrell L.J. Kaye GI (1995), Histology A text and atlus. Ross. M.H, Romrell L.J, Kaye G.I (edi) 3rd edition, Williams and Wilkins, P 696.

87 Sakuma S (1970) Glykogengehalt und-verteilung in der Uterusschleimhaut der Frau wahrend des normalen Zyklus im elektronenmikroskopischen Blid. Beitr Pathol Anat 140:454

88 Schmidt-Matthiesen H (1962a) Histochemische Untersuchungen der Endometrium-Ground substanz. Acta Histochem (jena) 13:129

89 Schmidt-Matthiesen H (1962b) Die Vascularisierung des menschlichen Endometriums. Arch Gynakol 196:575

90 Scholls, Lippman M. E. (1984), The estrogen receptor in MCF – 7 cells : evidence from dense amino acid labeling for rapid turn over and a dimeric model of activated nucleic receptor. Endocrinology 115 : 1295.

91 Shutter J et al 2005 Int. J Gynecol Pathol. 2005 Oct 24(4) 313-8.

92 Stanley J Robboy, Peter Russel, Malcom C, Anderson, Book of Gynaecological Pathology 304-314.

93 Stefan Visoki General Hospital, Smedervska Palanka, Sr P Arh Celok Lek 2002. Nov-Dec; 130 (11-12); 386-8. Results of Histopathologic findings of endometrial changes in metrorrhagia.

94 Stieve H (1952) Angeblich sterile Zeiten im Leben geschlechtstuchtiger Frauen.Z Geburtshilfe Gynakol 136:117.

95 Strott C A, Cargille C M, Ross G T, Lipsett M B, (1970) The short luteal phase. Journal of Clinical Endocrinology 30: 246-251.

96 Studzinkiz et al Study Ginegol Pol 2000 Max:71(3): 123-9. The Analysis of the co-existance of endometrial carcinan and uterine myoma.

97 Studzinskiz et al (Ginekol Pol. 1998 May 69/5) 273-8.

98 Szajnbok Sobrinto M, Goncalves WJ, Nicolau SM. Novone, De Lima GIR. Rev Paul Med 1990. Nov-Dec; 108(6): 252-6. (Pathology associated with uterine leiomyoma. Review of 600 cases)

99 Takamizawa S, et el. Gynecol obstet Invest 1999:48/3 (93-6).

100 Tamaya T, Motoyama T, Ostino Y, Ide NT, Surusaki T, Okaka H. Estradiol H beta Progesterone and 5 alphadihydrotestosterone receptors of uterine myometrium and myoma in the human subject. Journel of steroid biochemistry 1978;10:615-622.

101 Taubert H D (1978) Luteal phase insufficiency. Contributions to Gynecology and Obstetrics 4: 78-113.

102 Teleman S, Mihailovici MS Rev Med Chir Soc Med Nat Iasi- 2003 Apr-Jun; 107 (2): 379-82.

103 Telinde text book of Surgical Gynaecology 8 Edition; 731-765

104 Thomas JS Jr, Clark JF. Natl Med Assoc. 1989 Sep; 81(9); 969-72.

105 Todorovic N et al study 2002. Srp Arch Celok Lek 2002. Nov-Dec, 130(11-12). 386-8.

106 Treloar A.E., Boynton R.E., Benn B.A. and Brown B.W. (1967). Variation in the human menstrual cycle through out reproductive life. Int J fertil 12, 77 – 126.

107 Tsalacopouls H, Tiltman AJ, 1981. Gynaecol Obstet Invest. 1997; 44(4):275-7

108 Tsukahara Y, Fukamatsu Y, Sakai Y, Tomita K, Fukuta T, Nippon Sanka Fujinka Gakkai Zasshi 1983 Feb; 35(2); 207-12. A Clinicopathologic study of glandular cystic hyperplasia of the endometrium.

109 Ugwumadu AH, Harding K. Eur J. Obstet Gynecol Reprod Biol. 1994 Apr; 54(2); 153-6.

110 Vaezcy L, Scipiades E (1949) New Considerations in histologic examinations of the endometrium in connection with sterility. Gynaecologia (Basel) 128:260

111 Wang P et al Zhonghue Liu Xing Bing Xue Zazhi 1990 Dec; 11(6) 356-9. A Case control study on endometrial carcinoma

112 Wetzstein R. Wagner H (1960) Elektronenmikroskopische Untersuchungen am menschlichen Endometrium. Anat Anz 108:362.

113 Wiad Lek. 1993 Aug; 46(5-16):592-6. Related Articles, Links Articles in Blish. T Katedry I Kliniki Poloznichva I Ginekologli W Bytomics

114 Wiegand R (1930) Systematische histologische Untersuchungen uber die Arterien des Uterus. Z Mikrosk Anat Forsch 20:433.

115 Williamson EO. Christopherson WM. Malignant mixed mullercan tumors of the uterus cancer 1972;29;585-592.

116 Wisklocki GB. Dempsey EW (1945) Histochemical reactions

117 Witherspoon et al; J Clin Path., 1970, 23, 676-680 Endometrial changes associated with myomata of the uterus

118 Y in H, Mittal K, Int J Gynecol Pathol 2004 Jan 23(1) I 26.8. Incidental findings in uterine prolapse specimen.

119 Y in H, Mittal K, Int J Gynecol Pathol 2004 Jan 23(1):26.8 incidental findings in uterine prolapse specimen

120 Zentrial Gynatol 1982:104(13): 809-17. characterization of the endometrium in patients with uterine myoma.

121 Zheleznov BZ, Brumshtein LM. Akush Ginekol (Mask) 1990. fels: (2); 21-4