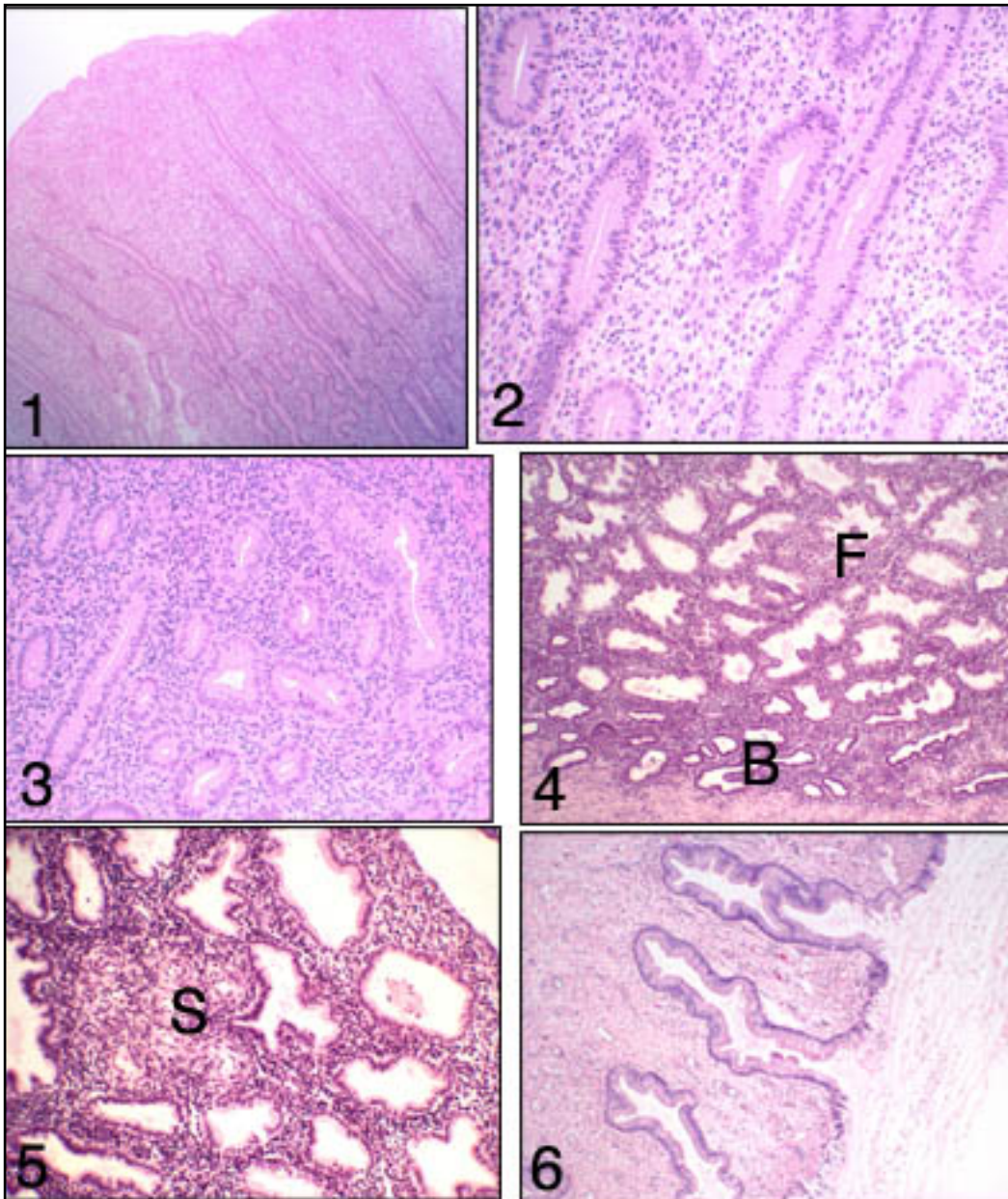


Uterus



1. Endometrium. Proliferative phase.
2. Endometrium. Proliferative phase. Note the straight profiles of the uterine glands and the nature of surrounding stroma. Both exhibit mitotic figures.
3. Stratum basale of endometrium. Proliferative phase.
4. Endometrium. Secretory phase. Compare and contrast stratum basale (B) and stratum functionale (F).
5. Spiral arteries (S) in endometrium at secretory phase.
6. Endocervix.

The human uterus is a single, hollow, pear-shaped organ with a thick muscular wall; it lies in the pelvic cavity between the bladder and rectum. The nonpregnant uterus varies in size depending on the individual but generally is about 7 cm in length, 3 to 5 cm at its widest (upper) part, and 2.5 to 3.0 cm thick. It is slightly flattened dorsoventrally, and the luminal cavity corresponds to the overall shape of the organ. The uterus receives the fertilized ovum and nourishes the embryo and fetus throughout its development until birth. Several regions of the uterus can be distinguished. The bulk of the organ consists of the body, which comprises the upper expanded portion. The dome-shaped part of the body between the junctions with the oviduct constitutes the fundus. Below, the uterus narrows and becomes more cylindrical in shape: this region forms the cervix, part of which protrudes into the vagina. The cervical canal passes through the cervix from the uterine cavity and communicates with the vaginal lumen at the external os. The wall of the uterus is made up of several layers that have specific names: the internal lining or mucosa is called the endometrium; the middle muscular layer forms the myometrium; and the external layer is referred to as the perimetrium. The perimetrium is the serosal or peritoneal layer that covers the body of the uterus and supravaginal part of the cervix posteriorly and the body of the uterus anteriorly.

Myometrium

The bulk of the uterine wall consists of the myometrium, which forms a thick coat about 15 to 20 mm in depth. The myometrium consists of bundles of smooth muscle cells separated by thin strands of connective tissue that contain fibroblasts, collagenous and reticular fibers, mast cells, and macrophages. The muscle forms several layers that are not sharply defined because of the intermingling of smooth muscle cells from one layer to another. Generally, however, internal, middle, and outer layers of smooth muscle can be distinguished. The internal layer is thin and consists of longitudinal and circularly arranged smooth muscle cells. The middle layer is the thickest and shows no regularity in the arrangement of the smooth muscle cells, which run longitudinally, obliquely, circularly, and transversely. This layer also contains many large blood vessels and has been called the stratum vasculare. The outer layer of smooth muscle consists mainly of longitudinally oriented cells, some of which extend into the broad ligament, oviducts, and ovarian ligaments. Elastic fibers are prominent in the outer layer but are not present in the inner layer of the myometrium except around blood vessels. In the nonpregnant uterus, the smooth muscle cells are 30 to 50 μm long, but during pregnancy, they hypertrophy to reach lengths of 500 to 600 μm or greater. New smooth muscle cells are produced in the pregnant uterus from undifferentiated cells and possibly from division of mature cells also. The connective tissue of the myometrium also increases in amount during pregnancy. In spite of a total increase in muscle mass, the layers are thinned during pregnancy as the uterus becomes distended. After delivery, the muscle cells rapidly decrease in size, but the uterus does not regain its original, nonpregnant dimensions. The myometrium normally undergoes intermittent contractions that, however, are not intense enough to be perceived. The intensity may increase during menstruation to result in cramps. The contractions are diminished during pregnancy, possibly in response to the hormone relaxin. At parturition, strong contractions of the uterine musculature occur, causing the fetus to be expelled. Uterine contractions increase in response to or after administration of oxytocin. This hormone is synthesized by neurons forming the supraoptic and paraventricular nuclei of the hypothalamus and released at the neurohypophysis. Uterine contractions also increase in response to prostaglandins. A rise in the level of prostaglandins occurs just prior to delivery.

Endometrium

The endometrium is a complex mucous membrane that, in women, undergoes cyclic changes in structure and function in response to the ovarian cycle. The cyclic activity begins at puberty and continues until menopause. In the body of the uterus, the endometrium consists of a thick lamina propria (endometrial stroma) and a covering epithelium. The stroma resembles mesenchymal tissue and consists of loosely arranged stellate cells with large, round or ovoid nuclei supported by a network of fine connective tissue in which lymphocytes, granular leukocytes, and macrophages are scattered. There is no submucosa, and the stroma lies directly on the myometrium, to which it is firmly attached. The stroma is covered by a simple columnar epithelium that contains ciliated cells and nonciliated secretory cells. The epithelium dips into the stroma to form numerous uterine glands that extend deeply into the stroma, occasionally penetrating into the myometrium. Most are simple tubular glands, but some may branch near the muscle. There are fewer ciliated cells in the glands than in the covering epithelium. A basement membrane underlies the glandular and surface epithelia. The endometrium can be divided into a stratum basale (basal layer) and a stratum functionale (functional layer), which differ in their structure, function, and blood supply. The stratum basale is the narrower, more cellular, and more fibrous layer and lies directly on the myometrium. Occasionally, small pockets of stratum basale may extend into the myometrium, between muscle cells. This layer undergoes few changes during the menstrual cycle and is not shed at menstruation but serves as the source from which the functional layer is restored. The stratum functionale extends to the lumen of the uterus and is the part of the endometrium in which cyclic changes occur and which is shed during menstruation. The stratum functionale sometimes is subdivided into the compacta, a narrow superficial zone, and the spongiosa, a broader zone that forms the bulk of the functionalis. The blood supply of the endometrium is unique and plays an important role in the events of menstruation. Branches of the uterine arteries penetrate the myometrium to its middle layer, where they furnish arcuate arteries that run circumferentially in the myometrium. One set of branches from these arteries supplies the superficial layers of the myometrium, while other branches, the radial arteries, pass inward to supply the endometrium. At the junction of myometrium and endometrium, the radial branches provide a dual circulation to the endometrium. Straight arteries supply the stratum basale, while the stratum highly coiled spiral arteries supply functionale. As the latter pass through the functional layer, they provide terminal arterioles, which unite with a complex network of capillaries and thin-walled, dilated vascular structures, the lacunae. The venous system forms an irregular network of venules and veins with irregular sinusoidal enlargements and then drains into a plexus at the junction of myometrium and endometrium. During menstrual cycles, the spiral arteries constrict periodically, subjecting the functional layer to intermittent periods of anoxia. The distal portions of the arterial supply in the functionalis undergo degeneration and regeneration with each menstrual cycle, whereas the straight arteries of the basal layer show no such changes.

Cyclic Changes in the Endometrium

During a normal menstrual cycle, the endometrium undergoes a continuous sequence of changes in which four phases can be described. The phases correlate with the functional activities of the ovaries and constitute the proliferative, secretory, ischemic (premenstrual), and menstrual phases. The proliferative phase begins at the end of the menstrual flow and extends to about the middle of the cycle. This stage is characterized by rapid regeneration and repair of

the endometrium. Epithelial cells in the remnants of the uterine glands in the stratum basale proliferate and migrate over the raw surface of the mucosa; stromal cells also proliferate. In the early part of this period, the endometrium is of limited thickness, and its glands are sparse and fairly straight and have small lumina. The epithelium of the glands and surface is simple cuboidal to low columnar, and mitoses are present in the glandular lining. As the proliferative phase advances, the endometrial glands increase in number and length and become more tortuous and more closely spaced, and the lumina widen. Toward the end of the proliferative phase (days 14-16), glycogen accumulates in the basal region of the glandular epithelium. The surface and glandular epithelia now are tall columnar with fewer ciliated and more secretory cells. The secretory cells have large numbers of small mitochondria, but the endoplasmic reticulum and Golgi complex are poorly developed. Microvilli are present on the free borders of the cells. The nuclei are round or oval and contain finely granular chromatin with one or more nucleoli. The spiral arteries lengthen but are lightly coiled and do not extend into the superficial third of the endometrium. The proliferative phase corresponds to the maturation of the ovarian follicle up to the time of ovulation. Estrogen, secreted by the developing follicles, stimulates growth of the endometrium; some growth may continue for a day or two after ovulation.

During the secretory phase, the endometrium continues to increase in thickness as a result of hypertrophy of stromal and glandular cells, stromal edema, and increased vascularity. The glands lengthen and become irregularly coiled and convoluted and show wide, irregular lumina. The epithelial cells become larger, and their free surfaces show many long microvilli. Mitochondria are large, there is a rich endoplasmic reticulum, and the Golgi apparatus is prominent. Nuclei are enlarged and contain distinct nucleoli. Glycogen and mucoid materials rapidly increase, first in the bases of the glandular cells, then in the apical portions of the cells, and then into the lumina of the glands. Elongation and coiling of the spiral arteries continue, and the vessels extend into the superficial part of the endometrium. The secretory phase is associated with development of a corpus luteum and is maintained as long as the corpus luteum remains functional. Progesterone secreted by the corpus luteum is the steroid primarily responsible for the secretory changes in the endometrium.

The ischemic (premenstrual) phase is characterized by intermittent constriction of the spiral arteries; resulting in vascular stasis and reduced blood flow to the functional layer. The outer zone of the endometrium is subjected to anoxia for hours at a time, resulting in breakdown of the stratum functionale. The stroma becomes increasingly edematous and infiltrated by leukocytes.

In the menstrual phase, the functional layer becomes necrotic and is shed. The spiral arteries also become necrotic, and blood is lost from the arteries and veins. Small lakes of blood form and coalesce, and overlying patches of mucosa are detached, leaving a denuded stromal surface. Sloughing of the endometrium continues until the entire functional layer has been discarded. Blood oozes from veins torn during the shedding of the endometrial tissue. The menstrual discharge consists of arterial and venous blood, autolyzed and degenerated epithelial cells, and glandular secretions. The straight arteries of stratum basale do not constrict during menstruation, thus preserving the basal layer to provide for restoration of the endometrium during the following new proliferative stage. The onset of the menstrual cycle coincides with the beginning involution of a corpus luteum.

Cervix

The wall of the cervix differs considerably from that of the body of the uterus. Little smooth muscle is present, and the cervical wall consists mainly of dense connective tissue and elastic

fibers. In the part that protrudes into the vaginal canal, smooth muscle is lacking. The cervical canal is lined by a mucosa, the endocervix, which forms complex, branching folds. The epithelial lining consists of tall, mucus-secreting columnar cells along with a few ciliated columnar cells. Numerous large, branched cervical glands are present that are lined by mucus-secreting columnar cells similar to those of the lining epithelium. The cervical canal usually is filled with mucus. Occasionally the glands become occluded and filled with secretion, forming Nabothian cysts. The portion of the cervix that protrudes into the vaginal canal, the exocervix, is covered by a nonkeratinized stratified squamous epithelium whose cells contain much glycogen. The transition from the simple columnar epithelium of the cervical canal is abrupt and usually occurs near the external os. The cervical mucosa does not take part in the dramatic cyclic changes that occur in the endometrial lining of the body of the uterus and is not shed. The glandular elements do show changes in secretory activity, however. At midcycle there is a copious secretion of a thin alkaline fluid, probably the result of increased stimulation by estrogen. After ovulation and establishment of a corpus luteum, the amount of secretion decreases and the mucus becomes thicker and more viscous. The lumen of the cervix is usually less than 1 cm in diameter but will expand to 10 cm or more at the time of birth. The dilatation is the result of increased elasticity and a softening of the cervical stroma during labor. The changes that occur within the cervical stroma are complex and not completely understood. However, changes are known to occur with regard to the making up of glycosaminoglycans in the ground substance during labor. Hyaluronic acid levels increase, binding more water, whereas concentrations of dermatan sulfate decrease, reducing the number of cross linkages between extracellular fibers within the stroma.

The net result of these changes is a softening of the matrix with a separation of connective tissue fibers. In addition, the collagen and elastic fibers within the stroma are shortened and rearranged in such a way as to decreased tensile strength and resistance allowing the dilatation to occur.