
2.1 Embryology

An in-depth discussion of embryology and anomalies of the female genital tract is beyond the scope of this text, and interested readers are referred to embryology texts; however, a brief review is in order. In the early first trimester, the external genitalia are not differentiated towards either gender. Both the Müllerian (paramesonephric) and Wolffian (mesonephric) ducts are present in parallel. Genetics determine which duct develops and which regresses. For XX individuals, the Müllerian ducts continue to develop, and the Wolffian ducts regress. Müllerian duct development relies on a number of genes in addition to absence of anti-Müllerian hormone (Müllerian inhibiting substance, MIS) [1], and the differentiation into a female is not merely becoming “not male.” Knock-out mice missing a variety of these female-determining genes have a variety of genital anomalies [1]. Differentiation of the embryo begins at about 8 weeks. The external genitalia and lower third of the vagina are formed by the urogenital sinus. The upper two thirds of the vagina, cervix, uterus, and fallopian tubes are formed by the fusion of the two Müllerian (paramesonephric) ducts. After fusion of the Müllerian ducts, the septum between them dissolves. When the urogenital sinus meets the Müllerian ducts, a vaginal plate is formed which subsequently canalizes, forming the patent and lined vagina. In a female, the Wolffian (mesonephric) ducts regress, but remnants may remain and be identified later in life.

The ovaries are indifferent in early embryonic life as well. At about 8 weeks of gestational age, the gonads can be reliably distinguished. This histologic distinction can be extremely important to make when examining an immature fetus from an unsuccessful or terminated pregnancy. Inexperienced clinicians and pathologists tend to mistake the external genitalia of late first/early second trimester female fetuses as male due to the prominence of the clitoris and not looking behind it to see the labia and patent vaginal opening rather than scrotum. Histopathology of the gonads can provide the gonadal gender (Fig. 2.1a, b). Migration of germ cells occurs along the midline along the dorsal mesentery of the hindgut [2], populating the ovaries, which

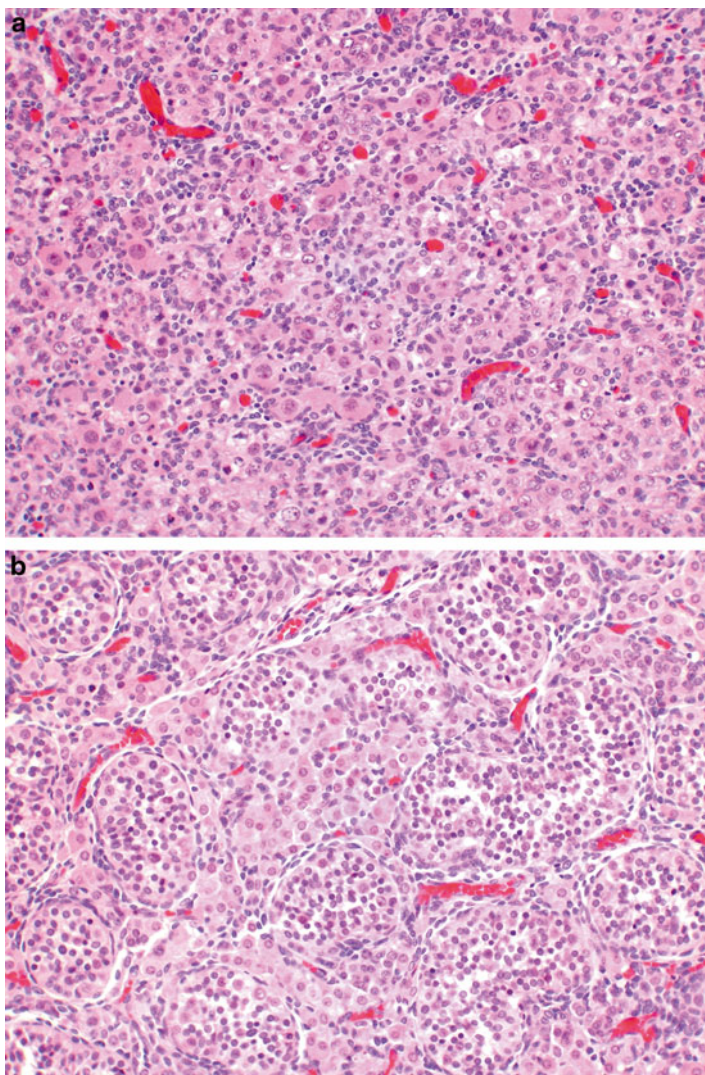


Fig. 2.1 Fetal gonads. The fetal ovary (a) shows diffuse distribution of germ cells. The fetal testis (b) shows distinct tubules containing Sertoli and germ cells, with intervening Leydig cells

are formed from the gonadal ridges [3]. It is because of this pattern of migration that germ cell neoplasms can occur anywhere in the body along the midline. No additional oogonia develop after birth, and some degenerate prior to birth, the rest enlarging prior to birth into primary oocytes, surrounded by a single flat layer of follicular cells forming the primordial follicle (Fig. 2.2). Therefore, a female is born with all the two to four million oocytes she will ever have. The maternal hormones may persist in the female infant, leading to cystic follicles (Fig. 2.3), which eventually regress in childhood until puberty. The XO fetus may occasionally show a streak gonad devoid of germ cells at birth, but germ cell loss may occur later (Fig. 2.4).

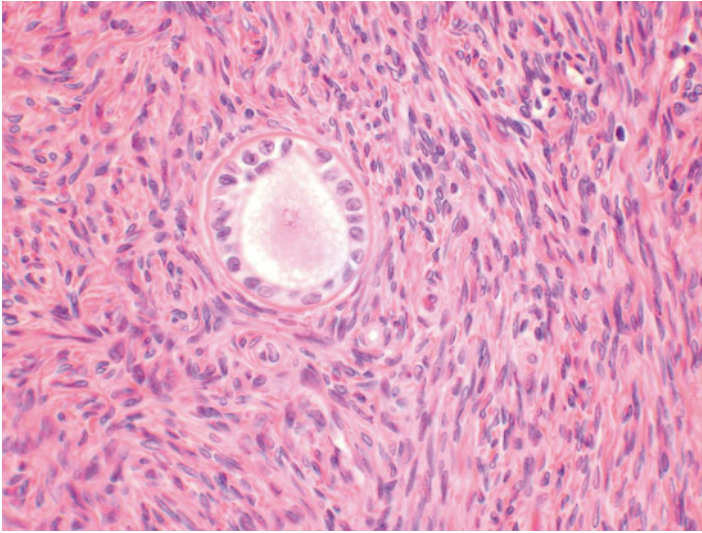


Fig. 2.2 The primordial follicle is composed of the ovum surrounded by a single layer of supporting follicular cells

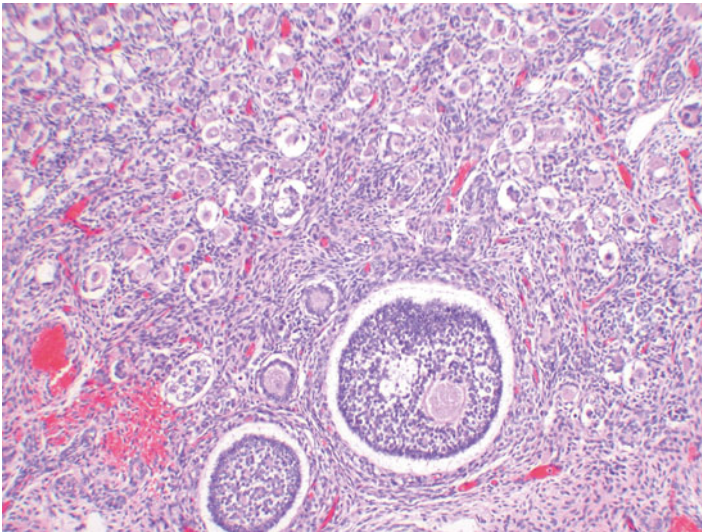


Fig. 2.3 The newborn ovary shows fewer primordial follicles than the fetal ovary, and follicular development as seen at the bottom of the image is a reflection of maternal hormonal effect

Aside from agenesis or hypoplasia, many of the anomalies of the female genital tract can be explained by defects in canalization of the urogenital sinus, or defects in either fusion of the Müllerian ducts or later dissolution of the intervening septum.

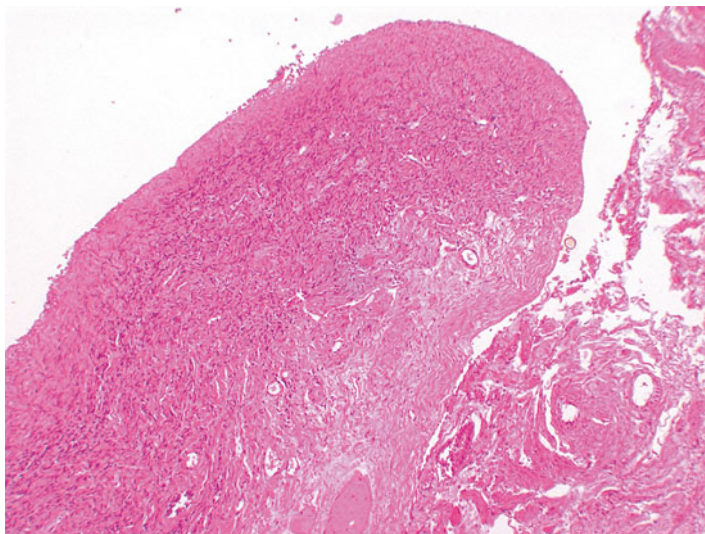


Fig. 2.4 Streak ovary devoid of germ cells

2.2 Histology of the Vulva

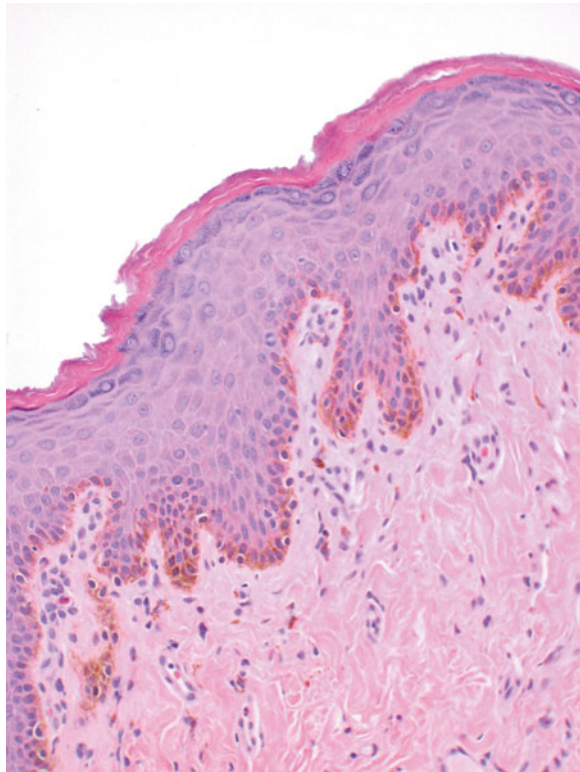
2.2.1 Labia Majora

The labia majora are similar to skin elsewhere on the body and are lined by a keratinized stratified squamous epithelium (Fig. 2.5). The dermis is less delineable into papillary and reticular dermis than skin elsewhere on the body, which is the basis of the modification of Clark's levels used for skin to vulvar Chung's levels for evaluating melanoma [4]. The labia majora contain hair follicles, apocrine, and eccrine glands confined to the outer portion of the labia majora only, and sebaceous glands in both outer and inner portions (Figs. 2.6, 2.7, and 2.8).

Labia minora—The labia minor are lined by squamous epithelium with a thin keratin layer outside, none inside, no hair, and fewer glands than the labia majora. These glands are comprised of sebaceous glands, with no apocrine or eccrine glands, hair follicles, or fat in the dermis. The dermis contains collagen and elastic fibers, blood vessels, and nerves.

Vestibule—The vestibule is the area above Hart's line, external to the hymen. Sebaceous glands end external to Hart's line, and there are generally no sweat glands in the vestibule. Minor vestibular glands comprised of acini lined by mucinous columnar epithelium may be present. The vestibule contains the openings of Bartholin's ducts, vagina, and urethra and is lined by a non-keratinized stratified squamous epithelium.

Fig. 2.5 Labia majora lined by keratinized stratified squamous epithelium. The basal pigmentation seen here corresponds to clinically appreciable pigmented skin



Bartholin's glands—The Bartholin's glands contain three types of epithelium. The glands are composed of acini lined by mucinous columnar epithelium. This merges in the ducts with a transitional epithelium and becomes squamous epithelium at the ostia which open onto the 4 o'clock and 8 o'clock positions of the vestibule (Fig. 2.9).

Clitoris—The clitoris is lined by keratinized stratified squamous epithelium, without dermal appendages. Erectile tissue is abundant beneath the epithelium and is composed of abundant vascular spaces (Fig. 2.10).

Perineum—The perineum is lined by keratinized stratified squamous epithelium. The perineum contains apocrine and mammary-like glands (Fig. 2.11). It used to be thought that there was accessory breast tissue along the milk line. This is now recognized as being anogenital mammary glands, which can also be present at the interlabial sulcus. These glands can give rise to neoplasms similar to those seen in the breast.

Mons pubis—The mons pubis is a fat pad covered by hair-bearing skin.

Hymen—The non-keratinized squamous epithelium of the hymen covers a loose fibroelastic tissue.

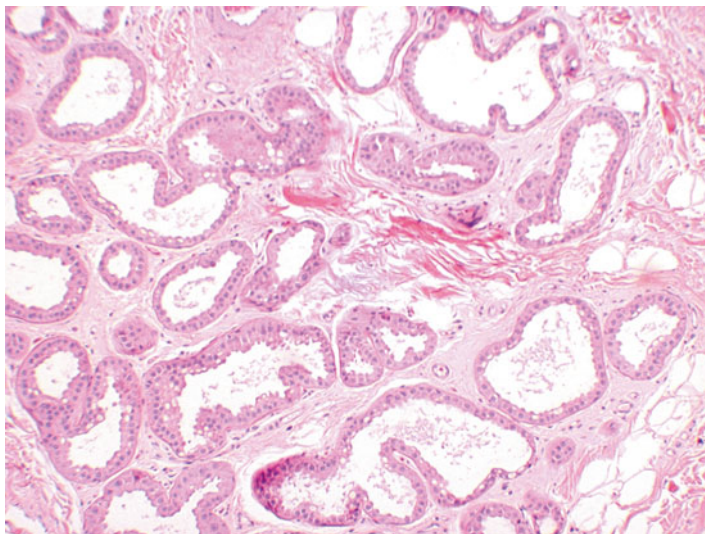


Fig. 2.6 Labia majora. Apocrine glands showing abundant eosinophilic cytoplasm

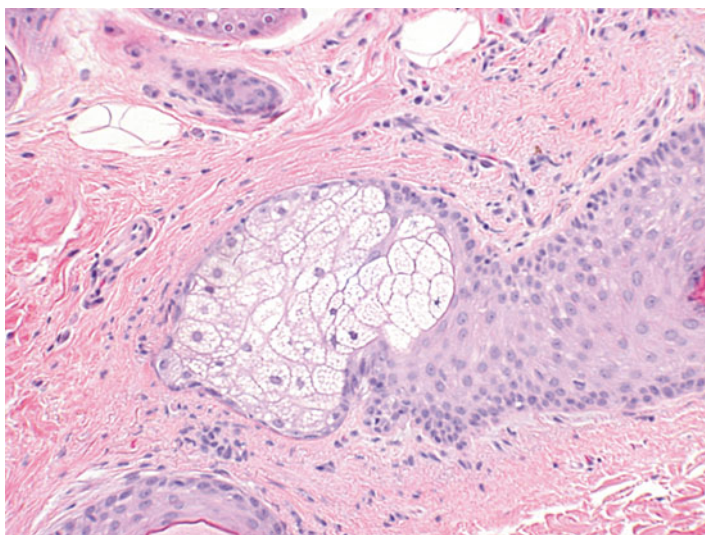


Fig. 2.7 Labia majora. A sebaceous gland is seen

Skene's ducts and glands—The Skene's glands are composed of mucinous columnar epithelium which drains via transitional ducts out on either side of the urethra, where the epithelium blends with the squamous epithelium of the vestibule. It is also thought that branches of the duct drain into the urethra. The Skene's glands are considered analogous to the male prostate.

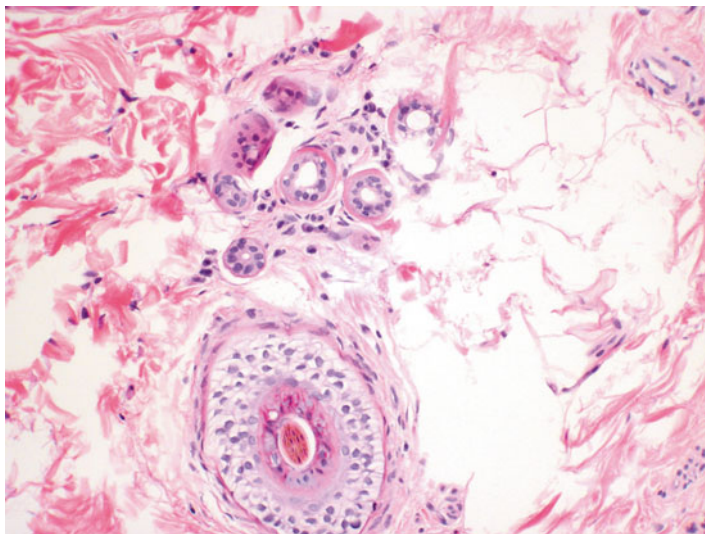


Fig. 2.8 Labia majora. A hair follicle is present at the bottom of the image, with eccrine glands above

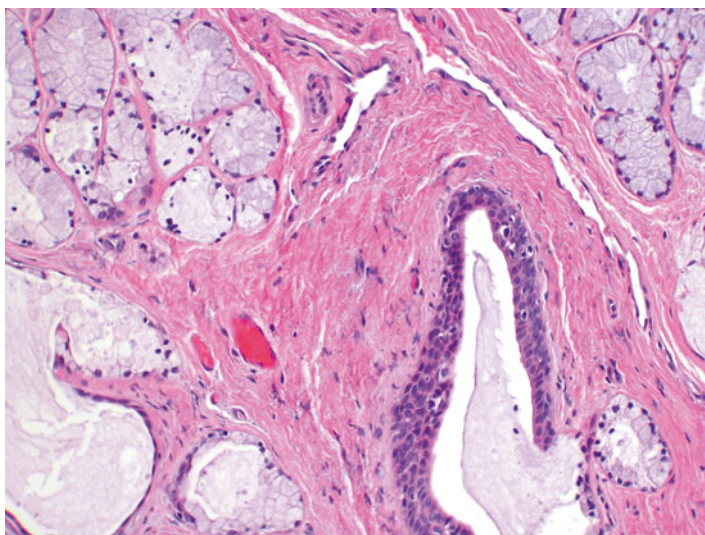


Fig. 2.9 Bartholin's glands show mucinous acini. A transitional epithelial-lined duct is seen at the bottom right

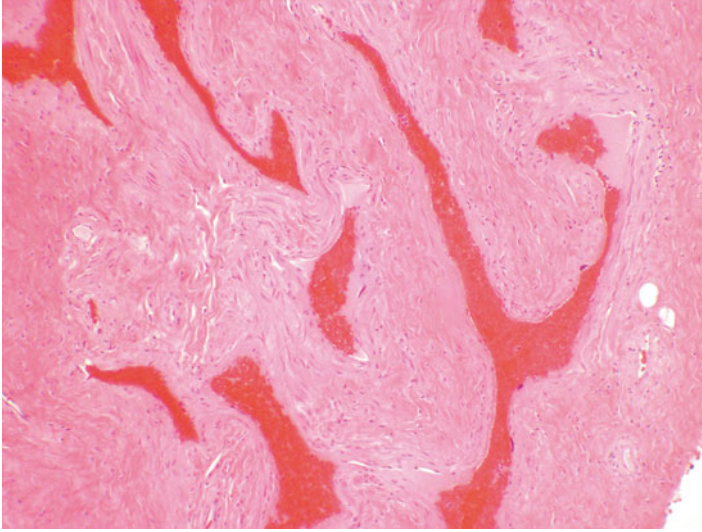


Fig. 2.10 Erectile tissue of the clitoris, containing numerous vascular spaces



Fig. 2.11 Mammary-like tissue of the vulva showing a ductal structure similar to breast

2.3 Histology of the Vagina

The vagina is lined by non-keratinized stratified squamous epithelium. During reproductive life, the epithelium is highly glycogenated due to the effect of estrogen (Fig. 2.12).

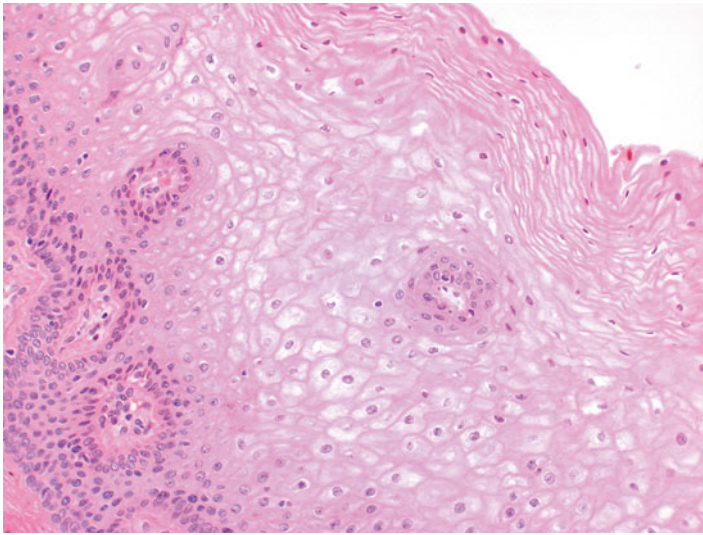


Fig. 2.12 The vagina is lined by non-keratinized stratified squamous epithelium containing abundant glycogen during reproductive life

2.4 Histology of the Cervix

2.4.1 Exocervix

The exocervix is lined by non-keratinized stratified squamous epithelium. The cells show an orderly maturation from the basal layer up to the surface, which shows impaired maturation when intraepithelial neoplasia is present. During reproductive life, the presence of estrogen leads to abundant glycogenation of the cells, which should not be mistaken for koilocytes in the absence of nuclear atypia (Fig. 2.13). Persistence of maternal hormones leads to similar glycogenated cervical epithelium in the neonate; however, in the child and menopausal woman, lack of estrogen leads to a more atrophic epithelium. With atrophy there is decreased glycogen in the cells, and the maturation from basal layer to surface is much decreased. This lack of maturation (Fig. 2.14) should not be confused with intraepithelial neoplasia. A Ki-67 immunostain (Fig. 2.15) can be used in difficult cases, because normal epithelium, including atrophic epithelium, will stain only in the parabasal layer, while neoplastic epithelium will stain up to the surface with this proliferation marker.

The epithelium overlies a stroma which is predominantly fibroconnective tissue, with small amounts of smooth muscle and elastin, which transitions into the myometrium in the lower uterine segment. Chronic inflammatory cells are common, and as this does not in most cases indicate a disease state, a diagnosis of “chronic cervicitis” is not appropriate (but used somewhat too liberally at times) unless the inflammation is severe with numerous lymphoid follicles or contains abundant plasma cells [5].

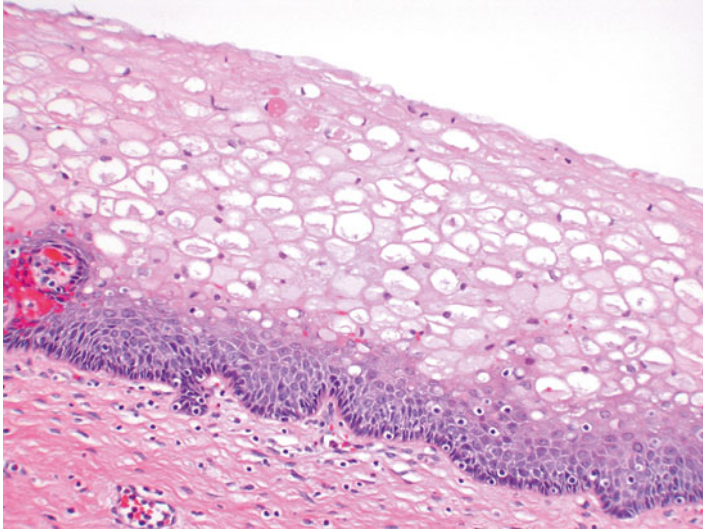


Fig. 2.13 Exocervix showing non-keratinized stratified squamous epithelium with abundant glycogen. Lack of nuclear atypia and orderly maturation rule out koilocytosis and intraepithelial neoplasia, respectively

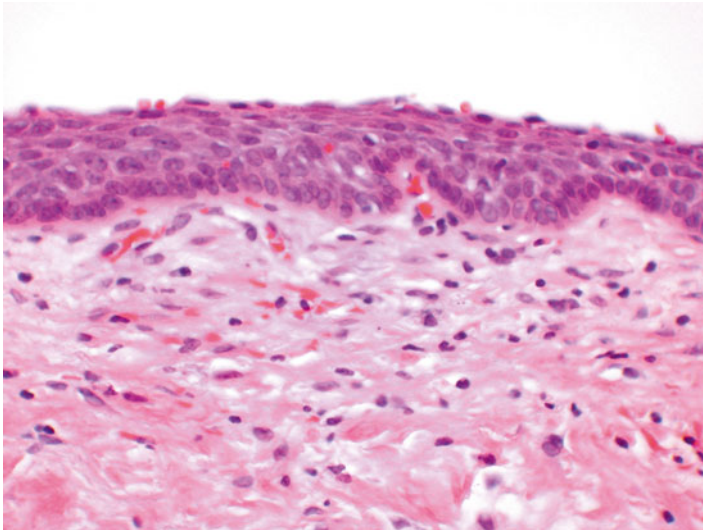


Fig. 2.14 Atrophic exocervix. Maturation and glycogen are decreased, but the cells are orderly

Remnants of the Wolffian ducts (mesonephric remnants) may frequently be seen in the lateral cervical stroma. These are recognizable by location (lateral, present about half way into the depth of the cervix) and by the epithelium, which is usually a flat cuboidal lining without cilia, with prominent eosinophilic luminal secretions frequent (Fig. 2.16).

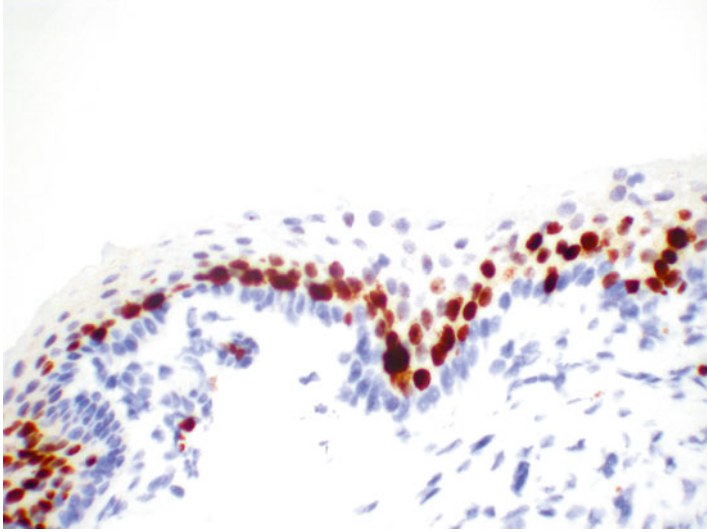


Fig. 2.15 Ki-67 immunostain in atrophy shows staining confined to the parabasal region

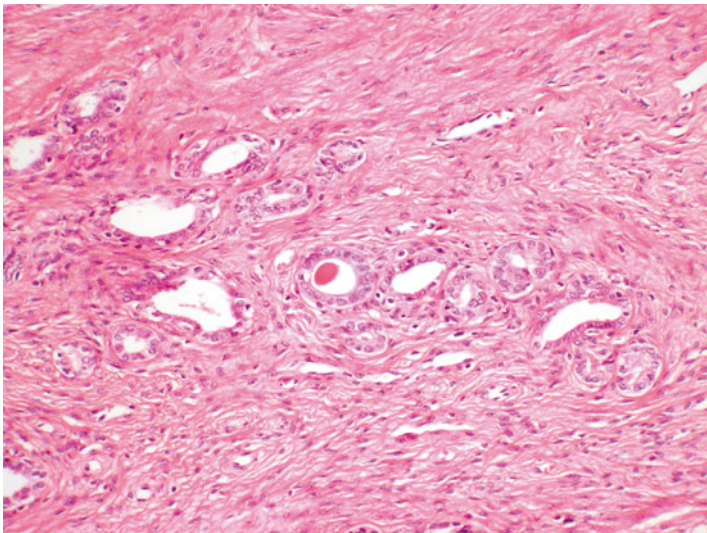
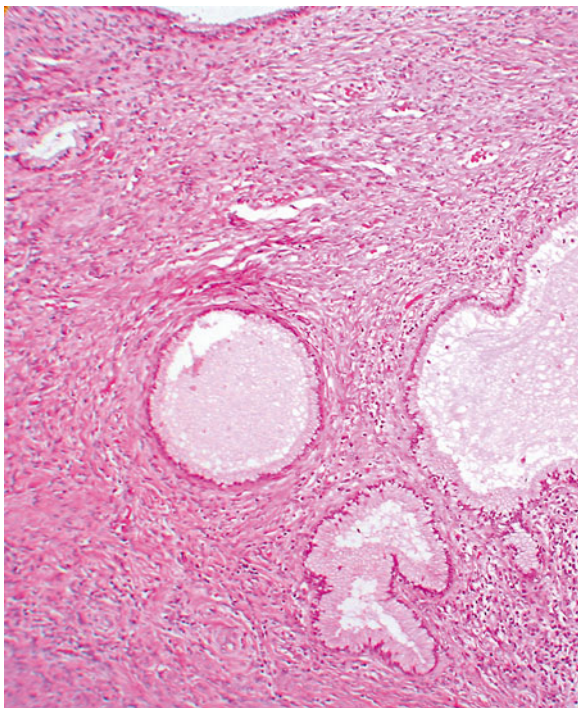


Fig. 2.16 Mesonephric remnants lined by cuboidal epithelium often show eosinophilic luminal secretions, as seen in the center

2.4.2 Endocervix

The endocervical crypts are branching crypts lined by mucinous columnar epithelium. On cross-section, they may appear as circular glands beneath the surface, but they communicate with the surface and produce cervical mucus (Fig. 2.17).

Fig. 2.17 Endocervical crypts may appear as glands, due to the orientation of the section, but communicate with the surface. Note the mucinous columnar epithelium with basal nuclei



2.4.3 Transformation Zone

The transformation zone is an area of interest as the zone where cervical neoplasia arises. It is the area between the original squamocolumnar junction and the current squamocolumnar junction. The squamocolumnar junction moves over the course of a woman's life. The original squamocolumnar junction is usually located on the exocervix in early reproductive life. The endocervix may then be seen on speculum examination, and in the past beefy pink tissue of the normal endocervix has been mistaken for "erosion." Squamous metaplasia occurs over time and goes up into the endocervical canal, establishing the woman's current squamocolumnar junction, which can be high up the canal in the older woman, making adequate colposcopy challenging. The area in between the original and current squamocolumnar junctions is the transformation zone. Metaplasia is the conversion of one benign epithelial type to another. Metaplastic squamous epithelium appears immature, and lacking in glycogen, but matures and acquires glycogen over time. Histology of the transformation zone may demonstrate an abrupt shift from squamous to columnar epithelium, or the squamous metaplasia may extend over a length. If endocervical crypts are blocked by squamous metaplasia and the secretions get inspissated, Nabothian cysts occur (Figs. 2.18, 2.19, and 2.20).

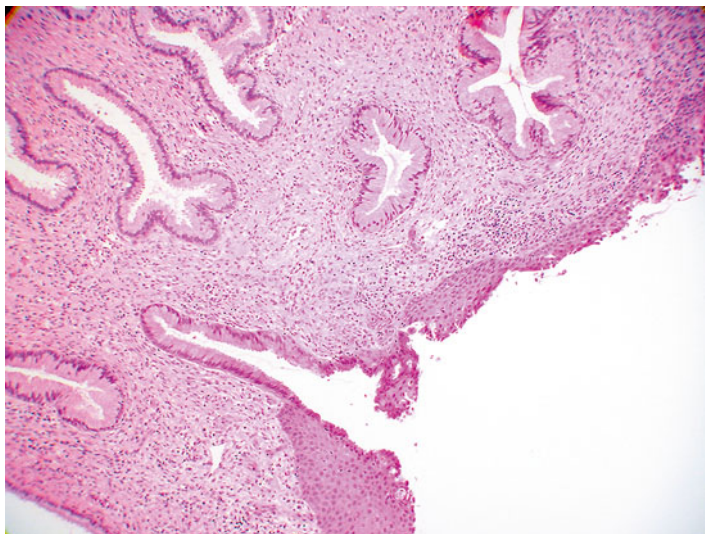


Fig.2.18 The transformation zone shows squamous metaplasia overlying endocervical crypts

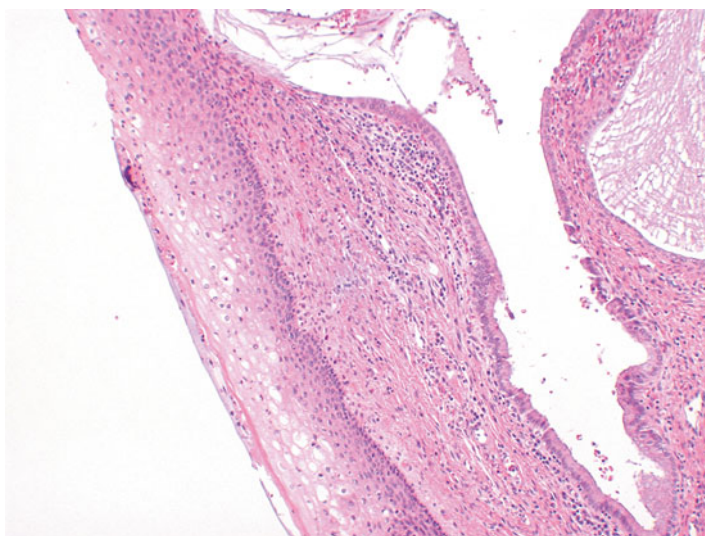


Fig.2.19 Transformation zone. Blocked endocervical crypts due to overlying squamous metaplasia can form Nabothian cysts, as seen to the right

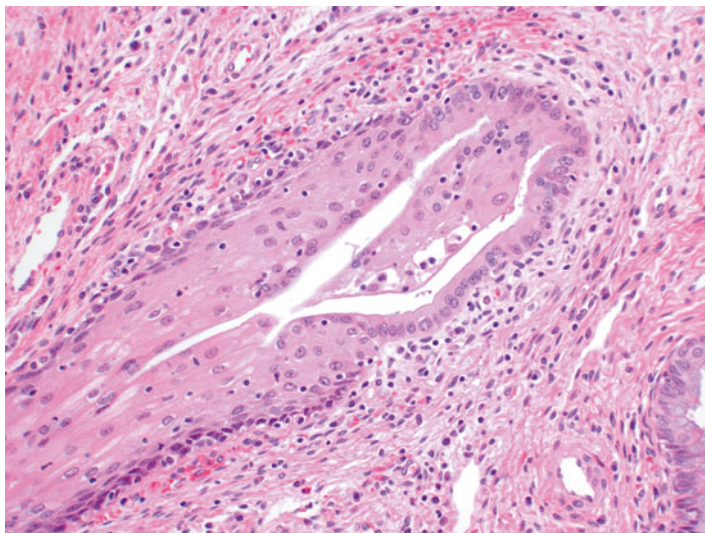


Fig. 2.20 Immature squamous metaplasia replacing an endocervical gland in the transformation zone

2.5 Histology of the Uterus

2.5.1 Endometrium

The endometrium is composed of a basalis layer, which remains behind after menses to regenerate, and a functional layer, which cycles with the ovarian cycle and sloughs at the end of each cycle that doesn't result in a pregnancy. In describing cycling endometrium histopathologically, the assumption is made that the cycle is 28 days, with days 1–5 being menses, as well as the initiation of the new cycle, day 14 is ovulation, and day 28 is the beginning of the next menses (i.e., day 1 again). This is of course not true for all women, and endometrial dating does not always correspond to fertility.

2.5.2 Proliferative Endometrium

Proliferative endometrium is present pre-ovulation (cycle days 1–14), due to the effect of estrogen alone. Proliferative endometrium (Figs. 2.21 and 2.22) is characterized by pseudostratification of the glandular epithelium. Although the glandular nuclei appear to be at different levels, all cells touch the basement membrane, hence the term “pseudo.” Mitotic figures are seen in the glands and stroma. The stroma is cellular, with

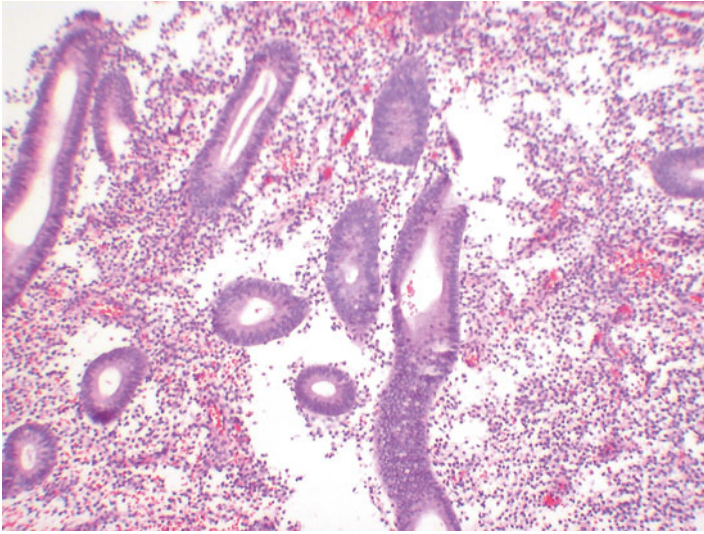


Fig.2.21 Proliferative endometrium showing fairly straight tubular glands lined by a pseudostratified epithelium with mitotic activity (*inset*)

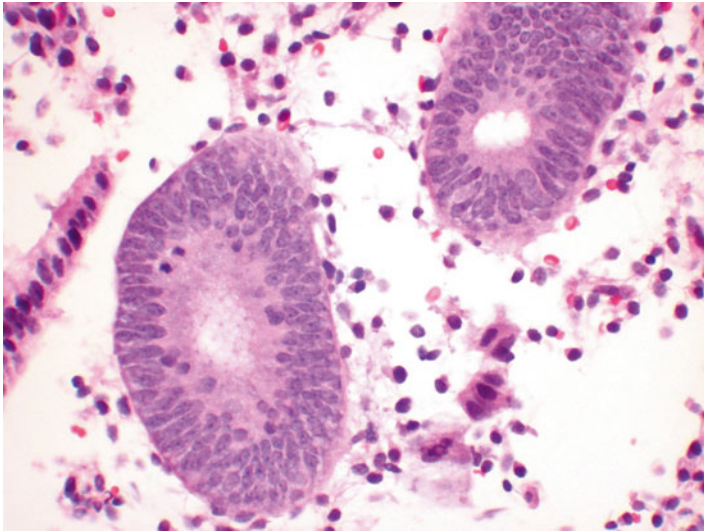


Fig.2.22 Proliferative endometrium. At higher power, the pseudostratification and mitotic activity (11 o'clock in the gland on the left) can be appreciated

small spindled nuclei. The glands are simple tubular glands in the early proliferative phase, becoming more complex in mid- and late proliferative phases. The stroma shows some edema mid-proliferative, but otherwise is not notably different during this time period.

Table 2.1 Dating the endometrium^a

Cycle day	Post-ovulatory day	Main distinguishing features
15	1	A few subnuclear vacuoles in a proliferative type endometrium
16	2	Subnuclear vacuoles in about half the glands
17	3	Uniform subnuclear vacuoles. First day ovulation can be confirmed by histopathology
18	4	Half subnuclear, half supranuclear vacuoles
19	5	Supranuclear vacuoles
20	6	Peak secretion
21	7	Early stromal edema
22	8	Peak stromal edema (“naked nuclei”)
23	9	Prominent spiral arterioles
24	10	Decidual cuffing around spiral arterioles
25	11	Decidua under surface
26	12	Spreading decidua, not uniform
27	13	Stroma entirely decidualized, inflammatory cells seen
28/1	14	Breakdown, new cycle begins

^aBased on the criteria of Noyes et al. [6]

2.5.3 Secretory Endometrium and Endometrial Dating

Secretory endometrium (cycle days 14–28) can be dated. The methodology has been around for a long time, as described by Noyes and colleagues in 1950 [6]. As there are more reliable methods of assessing the cycle, histologic dating of the endometrium has become less important in clinical practice. A brief review of the features is shown in Table 2.1. It should be noted that dating is not considered reliable in the presence of chronic endometritis.

The first day that a pathologist can reliably establish ovulation is day 17. The subnuclear vacuoles seen on days 15 and 16 are not uniformly present and may be due to estrogen alone. Changes from day 17 can be reliably interpreted as progestational effect along with estrogen. On day 17, subnuclear vacuoles are uniform, giving a piano key appearance. The glands are no longer pseudostratified, and mitoses are few, decreasing to almost none over the secretory phase (Fig. 2.23). The vacuoles migrate to the lumen, with half above and half below on day 18, and all above on day 19. Day 20 is peak secretion. At this point, the remainder of the changes seen are in the stroma. There is stromal edema beginning on day 21, peaking on day 22, giving a “naked nuclei” appearance. Stromal decidualization occurs for the rest of the cycle, spreading outwards. On day 23, spiral arterioles become prominent, with a thin layer of decidua around them (Fig. 2.24). This expands on day 24, and on day 25, decidua is seen under the surface epithelium. It continues to coalesce on day 26,

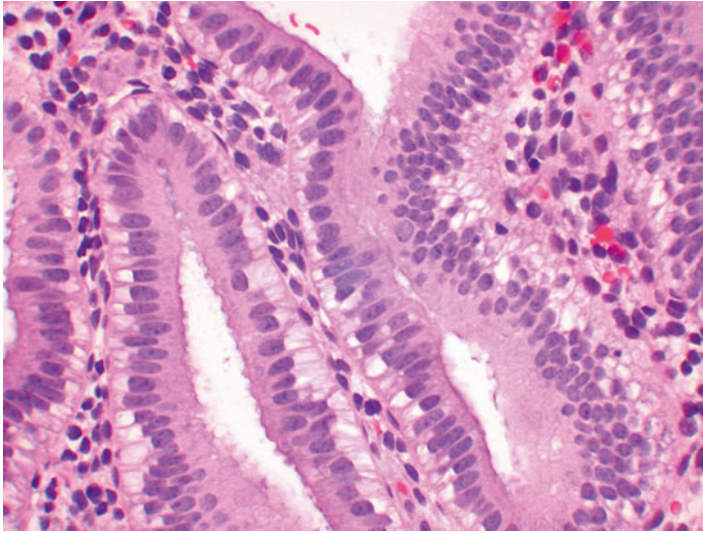


Fig. 2.23 Day 17 endometrium showing uniform subnuclear vacuoles in a “piano-key” configuration

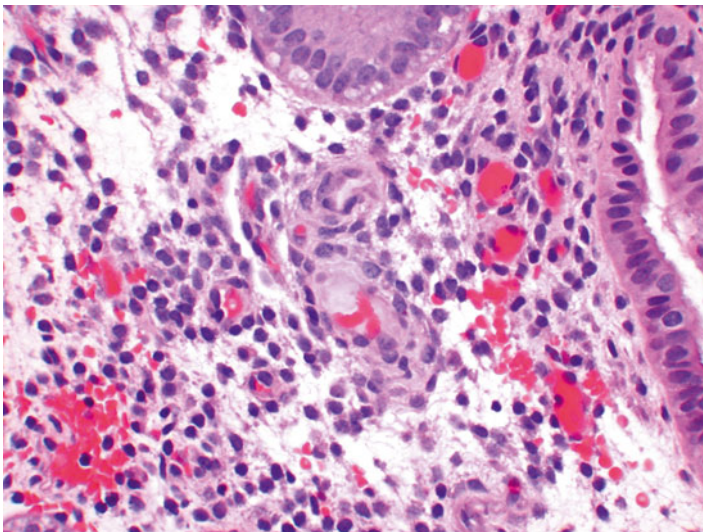


Fig. 2.24 Day 23 endometrium—Prominent spiral arterioles are seen in the center of the image

and by day 27 (Fig. 2.25), the stroma is entirely decidualized. Inflammatory cells, comprised of lymphocytes and neutrophils influx at the end of the cycle, and on day 28, breakdown begins, with thrombi in vessels, and gland-stromal dissociation (Fig. 2.26). If pregnancy doesn't ensue, there is repair, and a new cycle begins.

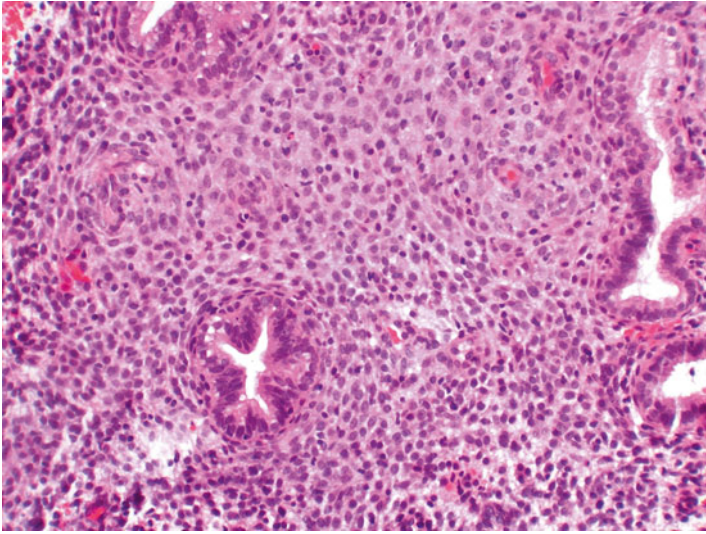


Fig. 2.25 Day 27 endometrium. Decidualization of stroma and secretory exhaustion of glands is present. Influx of inflammatory cells begins

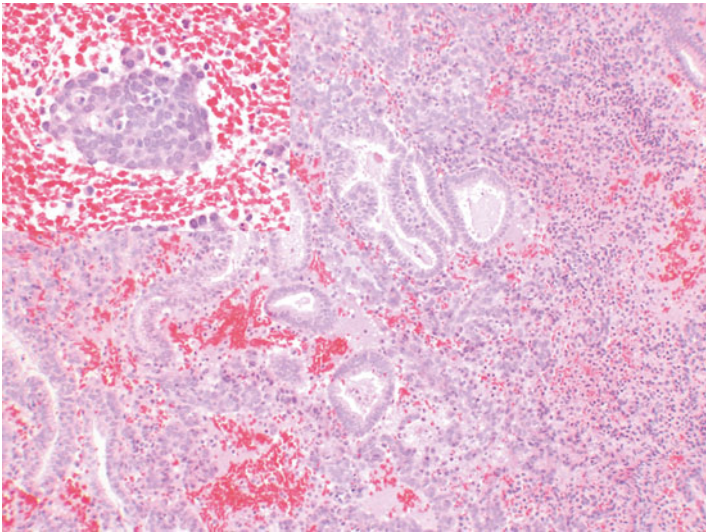


Fig. 2.26 Menstrual endometrium. Gland-stromal dissociation leads to formation of stromal "blue balls" (*inset*). With crumbling of the architecture, the establishment of whether ovulation occurred or determination of hyperplasia may not be possible

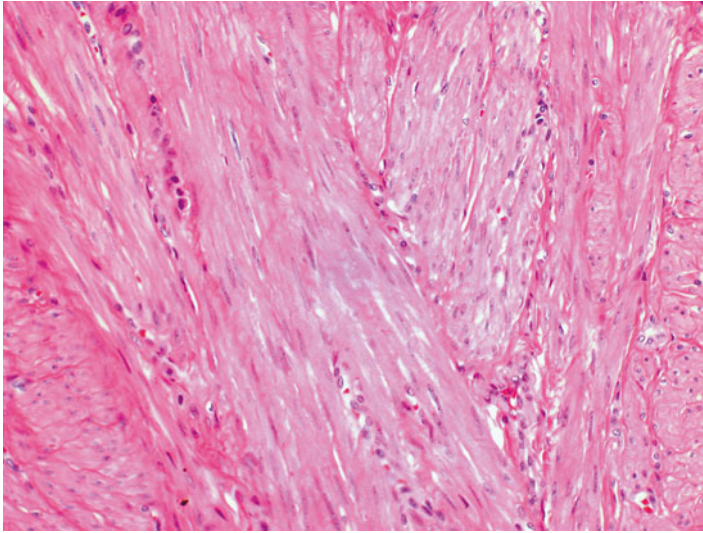


Fig. 2.27 Myometrium. Smooth muscle bundles extend in various directions

2.5.4 Myometrium

Myometrium is composed of predominantly smooth muscle, which is aggregated in bundles going in various directions (Fig. 2.27), along with some collagen and elastin. The cells have elongated cigar-shaped nuclei. Histologically, normal myometrium looks very much like leiomyomata on high power.

2.6 Histology of the Fallopian Tubes

The epithelium of the fallopian tube is mixed ciliated columnar, secretory nonciliated columnar cells with intercalated cells, which may represent a developmental stage of the secretory cells [5] (Figs. 2.28 and 2.29). The complexity of the infoldings of the fallopian tube varies by region, being prominent in the ampullary region. The individual folds are thin and delicate in the normal tube. The folds rest on two layers of smooth muscle, the inner circular and outer longitudinal. The cilia and muscle both work to transport the fertilized ovum to the uterine cavity.

2.7 Histology of the Ovaries

The lining of the ovaries, the surface epithelium, is derived embryologically from the same coelomic epithelium that forms the peritoneum. At ovulation, this surface becomes disrupted and may heal by invagination, forming small epithelial inclusion cysts.

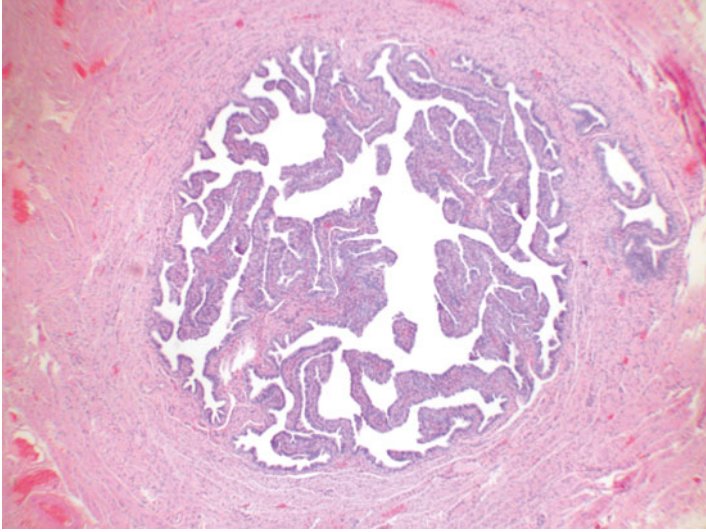


Fig. 2.28 Fallopian tube showing the delicate mucosal folds resting on a two layer muscular wall

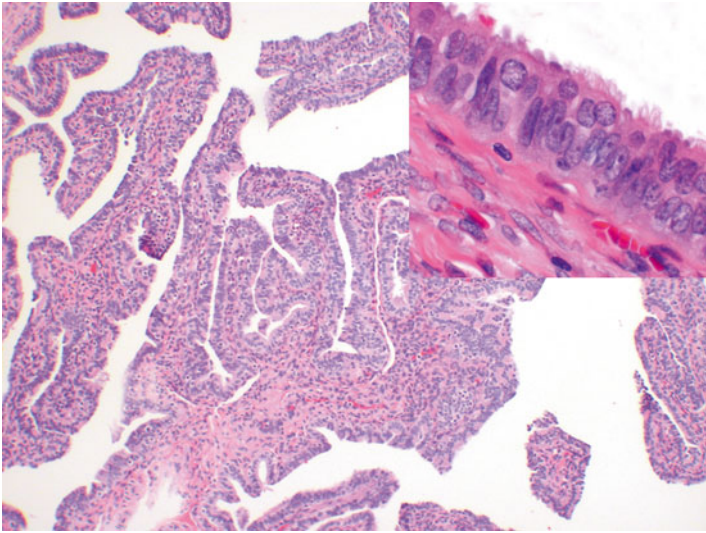


Fig. 2.29 Fallopian tube. At higher power, the delicate folds are seen to be lined by epithelium over a fibrovascular core. The epithelium is a combination of ciliated, secretory, and occasional intercalated cells (*inset right*)

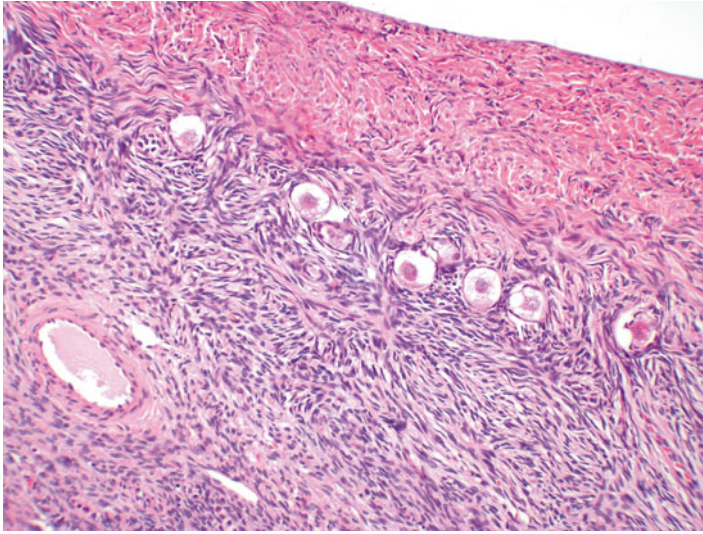


Fig. 2.30 Ovary showing primordial follicles in the spindle cell stroma of the cortex

These were previously thought to be related to the formation of epithelial ovarian carcinomas, particularly serous; however, malignant serous neoplasms are currently thought to arise from the fallopian tube fimbria [7]. The non-specialized ovarian stroma is a spindle cell stroma containing nerves and blood vessels. The specialized stroma, the granulosa cells and theca cells, surround the ova, forming the follicles. Normally, by adult life, the primordial follicles are much reduced and reside in the cortex (Fig. 2.30). A number of follicles are recruited each month; however, usually only one is destined to ovulate, although more than one may develop into an antral follicle (Fig. 2.31). After ovulation, the corpus luteum is formed. Grossly, this is yellow-orange in color, a reflection of the endocrine function. Histologically, the configuration is said to be cerebriform, mimicking the brain convolutions, and is composed of larger luteinized granulosa cells and smaller luteinized theca interna cells (Fig. 2.32) with central hemorrhage. Rarely, the corpus luteum may rupture and the hemoperitoneum may mimic a ruptured ectopic. If pregnancy does not occur, the corpus luteum regresses to become a corpus albicans, the name reflecting the gross white appearance. The corpus albicans retains the cerebriform configuration, but as these accumulate, they shrink down to small fibrous scars (Fig. 2.33). If pregnancy occurs, the corpus luteum of pregnancy, a somewhat larger structure, is formed.

2.8 Anatomy and Histology of the Placenta

The placental disk is comprised of a fetal surface and a maternal surface (Figs. 2.34 and 2.35). The fetal surface amnion and chorion extend in continuity with the fetal membranes of the gestational sac. The umbilical cord is usually inserted

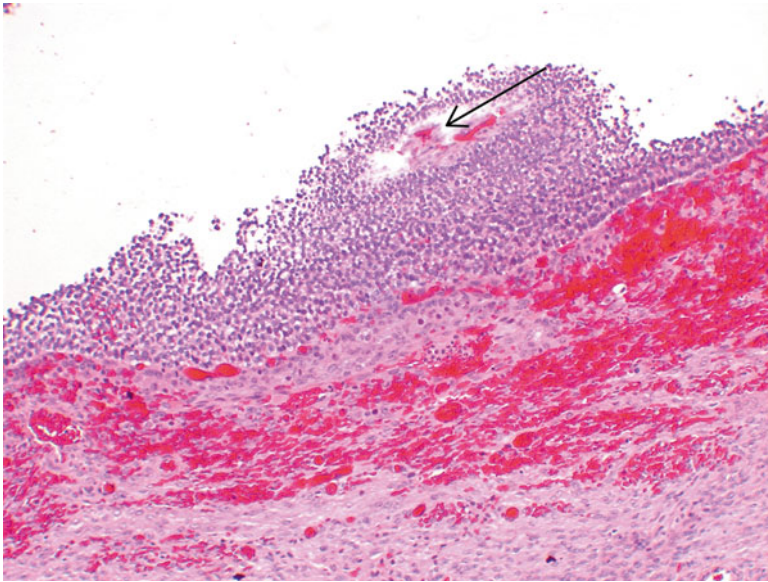


Fig. 2.31 Antral follicle. The antral space is above. The granulosa cells surround the ovum (*arrow* points to location of ovum, not well-visualized on this level) and form the inner lining of the antrum. The next layer is the vascular theca interna. The theca externa blends with ovarian stroma and is not well-delineated as a separate layer on sections

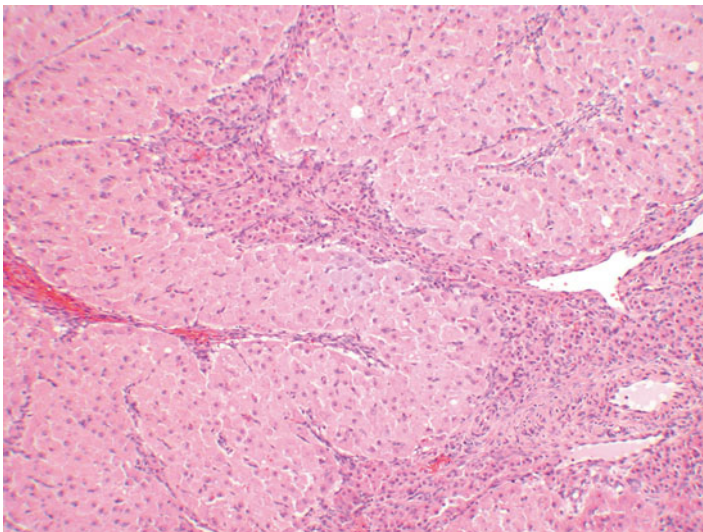


Fig. 2.32 Corpus luteum. The larger luteinized granulosa cells and smaller luteinized theca interna cells are arranged in a cerebriform configuration

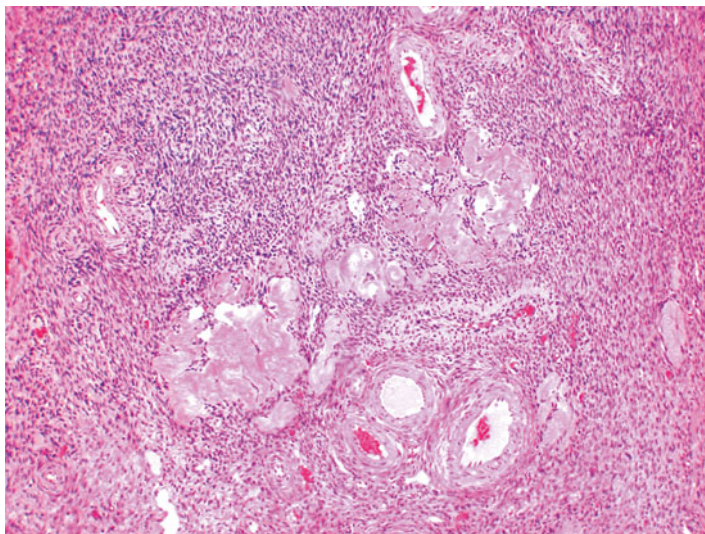


Fig. 2.33 Corpora albicantia retain the cerebriform configuration of the corpora lutea initially, eventually shrinking into small scars



Fig. 2.34 Fetal surface of the placenta. The paracentral cord is seen inserting into the membranes of the chorionic plate



Fig. 2.35 Maternal surface of the placenta showing intact cotyledons

paracentrally and arises from the fetal surface. On cross-section, the two arteries and single umbilical vein can be seen embedded in the protective Wharton's jelly. The parenchyma of the placenta is made up of chorionic villi. The space between the villi, the intervillous space, contains the maternal blood which provides oxygen and nutrients to the fetus. The maternal surface of the placenta is composed of cotyledons of placental tissue which implant into the maternal decidua. The decidua splits at birth, with a layer adherent to the maternal surface of the placenta. The decidua remaining in the uterus gives rise to the regenerating endometrium. During early placentation, physiologic conversion occurs, with the cells from the invading implantational intermediate trophoblast replacing the endothelium of the maternal spiral arterioles in the placental bed. This serves to convert the arterioles into passively patent venous channels. It is the absence of this physiologic conversion which is thought to be associated with later development of preeclampsia [8].

First trimester chorionic villi (Fig. 2.36) are larger than third trimester villi, which have continued to branch (Fig. 2.37). First trimester villi show a two cell layer, inner cytotrophoblast, and outer syncytiotrophoblast. Nucleated red blood cells may be seen in fetal vessels. These are most prominent at 8–12 weeks gestational age. Second trimester villi are intermediate in size, and the inner cytotrophoblast is mostly unapparent. Third trimester villi are smaller, and although still present, the cytotrophoblast is no longer seen on routine histology, leaving only the syncytiotrophoblast visible in histologic sections. Part of normal maturation is the formation of syncytial knots, which are the syncytiotrophoblast nuclei piling up as

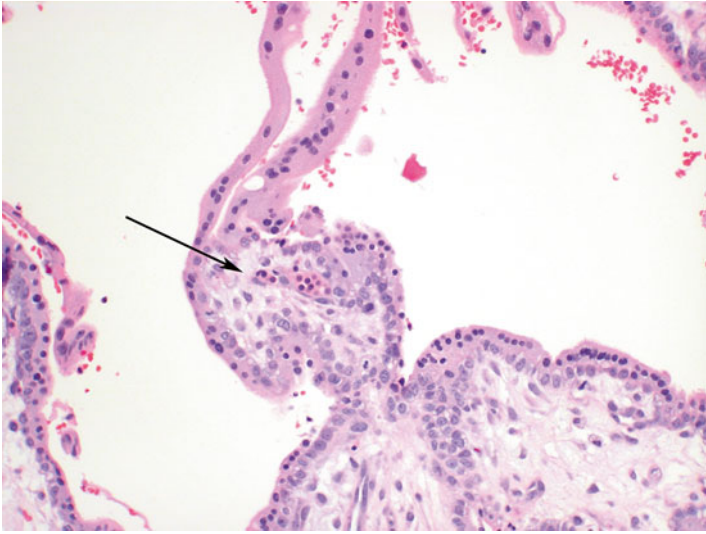


Fig. 2.36 First trimester chorionic villi show a two cell layer, inner cytotrophoblast, and outer syncytiotrophoblast. Nucleated red cells may be seen in a fetal vessel (*arrow*)

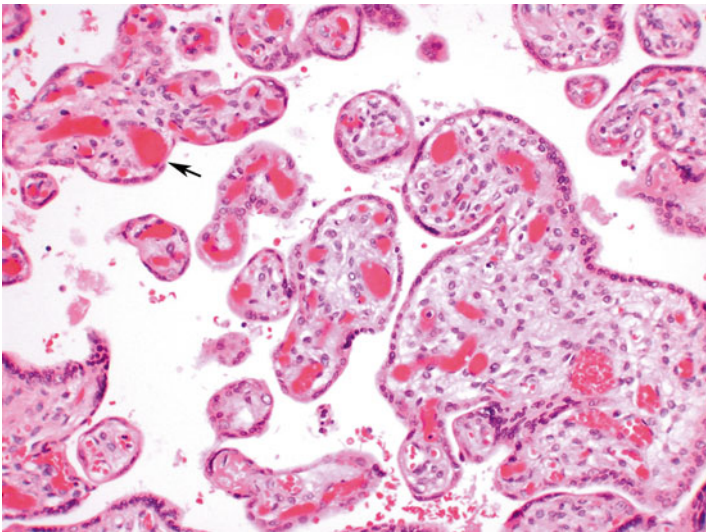


Fig. 2.37 Third trimester chorionic villi are smaller due to branching. A single syncytiotrophoblast layer is seen on sections. Villous capillaries are oriented peripherally in the villi, as close as possible to the maternal blood. The capillary, basement membrane of the villus, and attenuated syncytiotrophoblast cytoplasm form the “vasculosyncytial membrane” (*arrow*)

the cytoplasm of the syncytiotrophoblasts becomes attenuated over fetal capillaries of the villous stroma. These capillaries, which were more central earlier in pregnancy, are located more peripherally in the third trimester, to be closer to the maternal blood. The vessels, along with the attenuated syncytiotrophoblast cytoplasm, form the “vasculosyncytial membranes.” These are not true membranes, but the smallest interface between the fetal and maternal circulations, functioning analogously to alveolar septa.

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