Hormonal Biophysiology of the Uterus

Liane Deligdisch-Schor and Angelica Mareş Miceli

1 Uterine Development

The uterus is derived from the fusion of Müllerian ducts originating from the mesodermal genital ridge, starting at their caudal end and progressing up. This event starts in the invagination of coelomic epithelium, around the sixth week in utero (i.u.). Cervical glands appear by 15 weeks and endometrial glands as well as myometrial tissue around 19 weeks i.u. This development occurs under the influence of the maternal steroid sex hormones circulating from the maternal blood via the placenta into the fetal circulation. Müllerian duct development is normally inhibited in the male fetus by androgens and by a nonsteroidal hormone, Müllerian inhibiting substance (MIS) produced by the Sertoli cells of the testis [1, 2]. Congenital anomalies of the uterus are rare, mostly resulting from imperfect or absent fusion of the Müllerian ducts or atresia associated with an autosomal recessive or dominant genetic defect.

The endometrium at birth is usually at resting phase, inactive, and consists of a single layer of cuboidal epithelium with sparse glands surrounded by spindle-shaped stromal cells. Maternal hormonal influence however may elicit proliferative and secretory changes due to estrogenic and progesterone activity and even predecidual changes during intrauterine life with rare menstrual changes in the neonate. After delivery the endometrium normally reverts to its resting phase until menarche.

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The GnRH pulse generator is capable to induce ovarian follicle maturation and estrogen synthesis and secretion during intrauterine development of the female fetus and resumes this activity with the advent of menarche. At birth, with the acute loss of placental and maternal hormones, the neonate hypothalamus-placental-ovary system is released from negative suppression. It resumes secretion of GnRH stimulation and FSH and LH release for about the first 6 months of life, after which this secretion declines. Leptin, a substance produced in the adipocytes, plays an important role having the ability to activate the central elements controlling the hypothalamic pulse generator and the onset of puberty.

Puberty starts with nocturnal pulses of gonadotropin secretion with LH exceeding FSH, generating increase in serum estradiol which increments LH secretion by the anterior pituitary resulting later in full secretion of gonadotropins.

After a decade of quiescence, GnRH pulsatile secretion resumes at daytime, and gradually repetitive ovulatory cycles emerge. The ovarian steroid hormone secretion elicits a maturation process of the uterus: the corpus uteri grows first faster than the cervix, and the endometrium matures with established cycles of proliferation, secretion, and menstrual shedding following the cyclic stimulation and withdrawal feedback mechanisms of the pituitary-ovarian system.

Menarche usually occurs between 9 and 16 years of age, after secondary sexual characteristics have begun their development. The first menstrual cycles are usually non-ovulatory and irregular, with intervals of 2–3 months. Once regularly established the cycles last 3–6 weeks, with menstrual shedding occurring 2 weeks after ovulation. The preovulatory phase is variable, while the postovulatory phase is relatively constant. The menstrual blood flow including endometrial shed tissue lasts 2–7 days [3, 4].

2 Endometrial Cyclic Changes

The endometrial cavity is a roughly triangular collapsed space, with the apex opening at the bottom into the endocervical canal's upper and internal ostium; the lower and external ostium of the endocervical canal opens into the vaginal cavity. The continuity of the endometrial cavity and the vagina makes possible the periodic shedding of the endometrial functional layer and of menstrual blood.

During the reproductive period of life, the endometrium undergoes cyclic changes that vary between 21 and 42 days, with the average cycle lasting 28 days. In this model, ovulation is presumed to occur on day 14. "Dating" of the endometrium is based on the histological description of the endometrial tissues, glands, stroma, and blood vessels every day of the cycle, starting after the menstrual shedding. The cyclic structural changes of the endometrial tissue occur under hormonal influences which are cyclic as well and dependent on a delicate balanced interplay of stimulation, withdrawal, and feedback between anterior pituitary, nonsteroid hormones, and gonadal (ovarian) steroid hormones, depending on the central nervous system, mostly hypothalamic factors. Ovarian follicles are selected each month by promoting the growth of one and atresia of the other graafian follicles. This is due

to the secretion by the anterior pituitary lobe of follicular-stimulating hormone (FSH) during the stimulatory phase of the selected follicle. The granulosa cells in the follicles respond with the increase of their FSH receptors. The secretion of estradiol is related to granulosa aromatase synthesis depending on FSH arriving at the follicle and the ability of local estradiol to increase FSH receptors on follicle granulosa cells. FSH decline starts due to negative feedback at the preovulatory peak of increased estradiol and inhibin secretion. FSH-induced LH-receptor presence on the granulosa cells of the dominant follicle achieves LH stimulation at midcycle with subsequent progesterone synthesis on the cumulus and mural granulosa cells. LH initiates the process of ovulation and completion of meiosis, progressive luteinization of the follicle with granulosa cells shifting steroid synthesis to yield both estradiol and progesterone. Both enhance estradiol-positive feedback on GnRH pulse and anterior pituitary LH surge response. Eventually as the luteal phase progresses, progesterone-negative feedback acts to terminate the LH surge at both the pituitary and hypothalamic levels [5–8]. Gonadotropin releases at the maturation of the follicle are physiologically well coordinated based on feedback relationships, in the early follicle selection phase (FSH) and at ovulation (LH). The resulting "translation" by the endometrial tissue of hormonal cyclic stimulation and withdrawal is manifested at histologic examination by a prompt response consisting of a complex pattern of architectural and diversified cellular changes. "Dating" of these changes reflects the accuracy of adequate responses to hormones by the tissue destined to serve as a host to an implanting conceptus, thus securing the survival of the species.

The endometrial tissue lining the inner surface of the myometrium is composed of two layers: the basal layer and the functional layer. The basal layer lies on the myometrial tissue and is composed of basal glandular structures surrounded by stromal tissue containing blood vessels. It is poor in hormone receptors and does not display obvious structural changes during the menstrual cycle except for a partial shedding with the menstrual blood flow. During the reproductive life, the functional layer changes promptly exhibiting a wide variation of patterns involving glands, stroma, and blood vessels, with different aspects on every single day of the cycle, that can be assessed on endometrial biopsied tissue. During the preovulatory phase which lasts on average 14 days, but can be variable in its duration in otherwise normal cycles, the endometrium is proliferative under predominant estrogenic influence, and three consecutive patterns are described: early, mid-, and late proliferative endometrium. Specific histological patterns are expected to be seen on every single day of the postovulatory 14 days (for a summary of the histologic cyclic changes/"dating" of the endometrium, see Table 1).

The early proliferative phase starts with repair and regrowth of the endometrial tissues after menstrual shedding. Basal glands are proliferating from their bottom toward the surface, and the endometrial thickness increases up to tenfold during the preovulatory phase. The epithelial and stromal cells acquire estrogen receptors which are expressed during the proliferative and early secretory phase. The glands are tubular and straight lined by cuboidal to columnar epithelial cells in the early proliferative phase, become coiled in the mid-proliferative, and lined by columnar cells, and tortuous and pseudostratified in the late proliferative phase due to the

Table 1 Endometrial cyclic changes ("dating" of the endometrium)

Phase	Thickness	Glands	Epithelium	Nuclei	Stroma	Blood vessels	Mitoses
Early proliferative	1 mm	Straight tubular	Tall columnar	Centrally located mitoses nucleoli prominent	Abundant edema (day 8–10) scant cytoplasm (bare nuclei) mitoses	Thin straight inconspicuous	++
Mid-proliferative	8 mm	Coiled	Pseudostratified				
Late proliferative	10 mm	Tortuous					
Ovulation	12–15 mm	Tortuous coiled	Giant mitochondria	Plump, prominent chromatin	Edema	Thin, mildly coiled	+
Day 16	12–15 mm		Columnar, Subnuclear vacuoles	Middle third 50% "piano keys"	Spindle cells		+
Day 17	12–15 mm		Columnar, Supranuclear vacuoles	Middle third 90%			±
Day 18	12–15 mm	Intraglandular secretion	Frayed apical border	Basal			–
Day 19	12–15 mm		Cuboidal		Mild edema		–
Day 20	12–15 mm	Dilated, cystic					–
Day 21	12–15 mm	Dilated					–
Day 22	12–15 mm	Intraluminal secretion			Peak edema		–
Day 23	12–15 mm					Spiral arterioles	–
Day 24	12–15 mm				Perivascular decidua		–
Day 25	12–15 mm				Diffuse decidua		–
Day 26	12–15 mm	"Sawtooth" shape	Low cuboidal, exhausted				–
Day 27	8–10 mm		Apoptosis	Pyknotic	Leukocyte infiltrate breakdown	Fibrin thrombi	–
Day 28	2 mm	Disrupted secretory	Cell debris			Thrombosed	–
Early menstrual	1 mm		Apoptosis	Nuclear debris	Hemorrhage	Necrotic	–
Late menstrual	<1 mm	Necrotic					–

increase in size and numbers of the epithelial cells. Mitotic activity is also progressively increasing during the preovulatory phase. The nuclei of glandular epithelial cells are centrally located and display during early proliferation diffusely distributed chromatin. In mid- and late proliferative endometrium, the nuclei display coarse clumps of chromatin, and mitotic figures become frequent, located late in the apical region of the cells. Nucleoli are prominent, large, and complex. The apical border of the cell shows microvilli, and the cytoplasm contains abundant ribosomes reflecting the protein synthesis during the proliferative phase. The stroma is abundant, representing about half the volume of the endometrium, roughly equal to the volume of the glands. The stromal cells are spindle-shaped, with plump nuclei and scant cytoplasm; mitotic activity is present in the stroma along with that in the glands. There is stromal edema during the mid-proliferative phase, about on the eighth to tenth post menstrual day (Figs. 1 and 2). The blood vessels are rather inconspicuous, thin, and straight. Few hours after ovulation, the histologic appearance changes dramatically under the additional influence of progesterone secreted by the corpus luteum (Fig. 3). The endometrial tissue becomes more abundant, due to increase of stromal cells and edema. Histologically during the first postovulatory days, the endometrial glandular epithelium becomes secretory, first (day 16) showing subnuclear vacuoles (Figs. 4 and 5) which then, on the 17th day, become supranuclear. The epithelial cells on ultrastructure display giant mitochondria surrounded by loops of endoplasmic reticulum and glycogen accumulation in the sub- and supranuclear vacuoles (Fig. 6). The nuclei are pushed from their initial basal position to the middle third of the cell ("piano-key" image) and return on the 18th day to the basal position. During the proliferative phase, the endometrial surface is smooth; after ovulation, the secretory vacuoles are present in almost all (80–90%) cells lining all glands (Figs. 7 and 8). This is the histological evidence on endometrial biopsy that ovulation has indeed occurred and is an important finding in the work-up for infertility. By day 19–20, the vacuoles disappear from the cytoplasm being secreted at the luminal border into the glandular lumen. The apical border becomes frayed and the cell is cuboidal. No new mitoses are present in the glands during the secretory phase, except for those "leftover" during the first days from the proliferative phase. The stromal changes are most evident after day 20. Stromal edema is seen on day 21, reaching its peak on day 22, with stromal cells consisting of spindle-shaped nuclei and scant or visually absent cytoplasm (bare nuclei), while glands appear dilated, lined by a quiescent epithelium, containing abundant secretion in their lumen. On day 23 the vascular component of the endometrium, so far inconspicuous, becomes prominent with the appearance of spiral arterioles (Figs. 9 and 10). The coiled spiral arterioles increased in length and thickness and appear on histologic sections with multiple lumina, due to the coiling, with a markedly increased surface. This finding is important for the evaluation of the quality of the postovulatory endometrium. The coiled, increased surface of the endometrial arterioles offers more opportunity for a possible blastocystic trophoblast to tap into the maternal blood and achieve implantation. Endometrial biopsy evaluation for infertility assesses not only ovulation, evident as secretory glands, but its efficiency as a site of implantation, by the presence of well-formed spiral arterioles. On day 24 the

stromal cells surrounding the spiral arterioles become decidualized: they become plump, and their central nuclei are surrounded by cytoplasm which increases in volume. This change extends to the stroma beyond the perivascular zones, involving the entire stroma by day 25. The decidual cells form a mosaiclike pattern with a compact endometrial surface. The glands after day 24 are dilated and contain inspissated secretion; on day 26 the glands have a sawtooth appearance, and their lining epithelium appears exhausted. On day 27 numerous leukocytes appear in the stroma, and the glandular epithelium exhibits fragmented nuclear debris due to the apoptosis of the tissue. On day 28 there is a marked infiltration of the stroma by leukocytes, and breakup by apoptosis of endometrial tissue starts. Dissolution of endometrial glands and stroma follows the withdrawal of both estrogens and progesterone as a result of negative feedback. On endometrial biopsy of early menstrual endometrium, there are disrupted glands with secretory features, though mostly exhausted, lined by cuboidal cells. Fibrin thrombi are seen in the blood vessels and the stroma appears broken down and hemorrhagic. During the following days of menstrual shedding and bleeding, the glands collapse, the stroma is condensed, and the nuclei become pyknotic. Endometrial biopsies taken at this point do not show sufficient evidence whether the cycle was ovulatory or not.

Dating of endometrium is the identification of the day of the cycle from the microscopic pattern of endometrial biopsies. An accurate evaluation is possible due to the specific features that are characteristic for each postovulatory day and for most proliferative days. Diagnosing the presence and quality of ovulation from its endometrial tissue response is an important test for the adequacy of this tissue as a potential host for an implanting conceptus. Iatrogenic hormone therapy, mostly steroid sex hormone therapy, has an important influence on the endometrial micro-

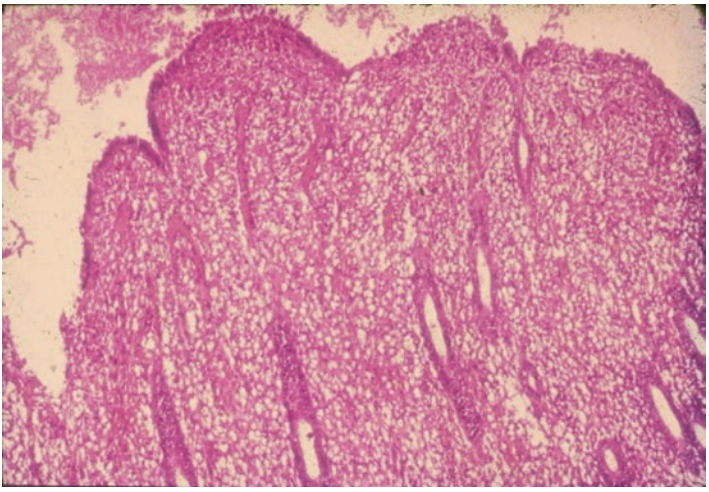

Fig. 1 Mid-proliferative endometrium: glands are straight, stroma edematous. H&E ×40

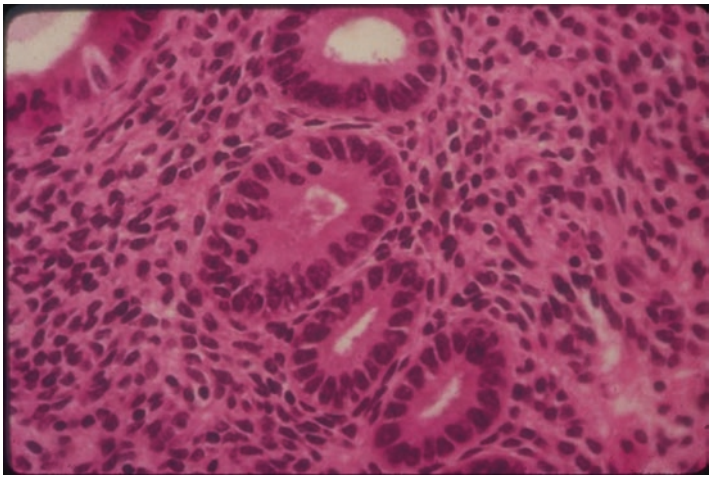

Fig. 2 Mid-proliferative endometrium: tubular glands. Mitotic activity in the glands H&E x 100

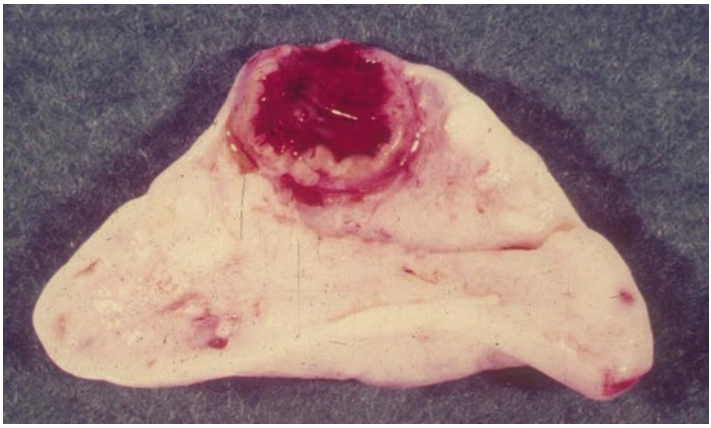

Fig. 3 Ovulating ovary with hemorrhagic corpus luteum

structure modifying the histologic patterns and often creating confusion when compared to the natural cyclic changes.

3 Uterus at Menopause

Menopause is characterized by the progressive diminution and eventual cessation of ovarian secretion of estrogen, due to failure to respond to gonadotropic hormones. Within a year after the final menstrual period, ovarian follicle exhaustion is complete. FSH and LH continue to rise with tripling of LH by 3 years postmenopause.

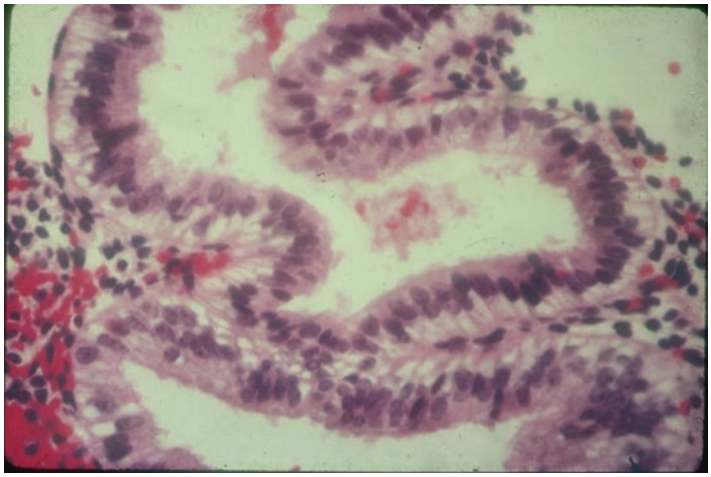

Fig. 4 Postovulatory endometrium: day 16–17 subnuclear vacuoles. H&E ×40

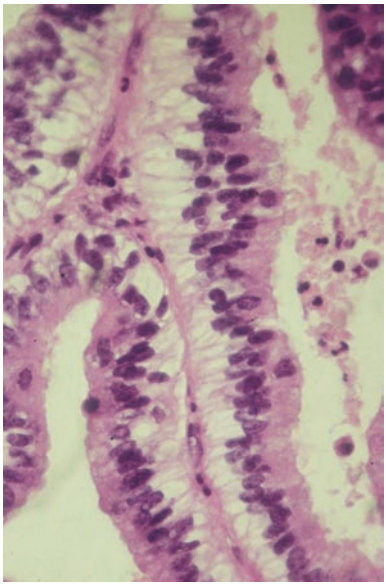

Fig. 5 Postovulatory endometrium, day 16–17. Subnuclear vacuoles, nuclei in middle third of cell, "piano-key" pattern H&E x100

Hypergonadotropism persists, although diminished [9]. In the absence of estrogen stimulation, the endometrium becomes thin, inactive (non-proliferative and nonsecretory), and gradually atrophic. The myometrium including possible leiomyomas is shrinking as well. The endometrium is thin, less than 1 mm. On endometrial biopsies the glands appear straight, tubular, and lined by cuboidal epithelium with centrally located round nuclei. No pseudostratification is present. Commonly seen are cystically dilated glands lined by flattened epithelium [10]. On ultrastructure the

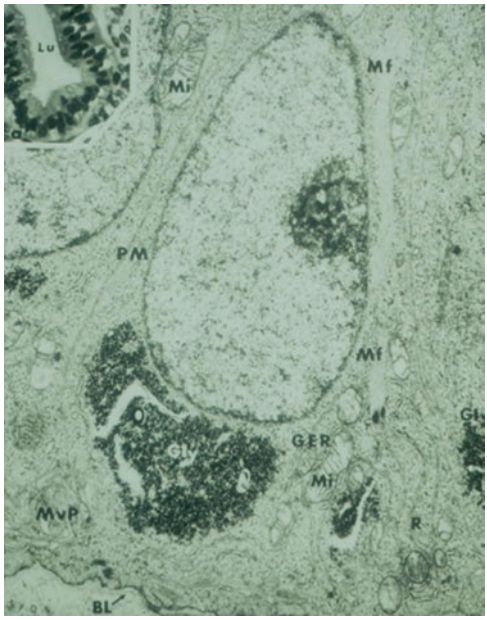

Fig. 6 Transmission electron microscopic image of postovulatory endometrium: subnuclear glycogen aggregates, prominent nucleolus, large mitochondria surrounded by endoplasmic reticulum, free cytoplasmic ribosomes

Fig. 7 Scanning electron microscopy: proliferative endometrium. Note smooth surface and glandular openings

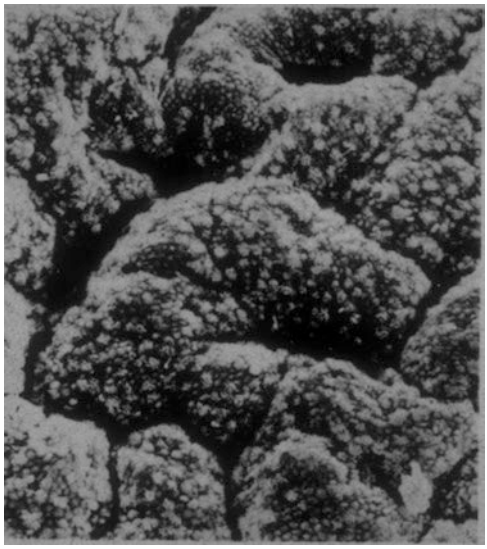

Fig. 8 Scanning electron microscopy: secretory endometrium, deeply folded surface covered by secretory granules

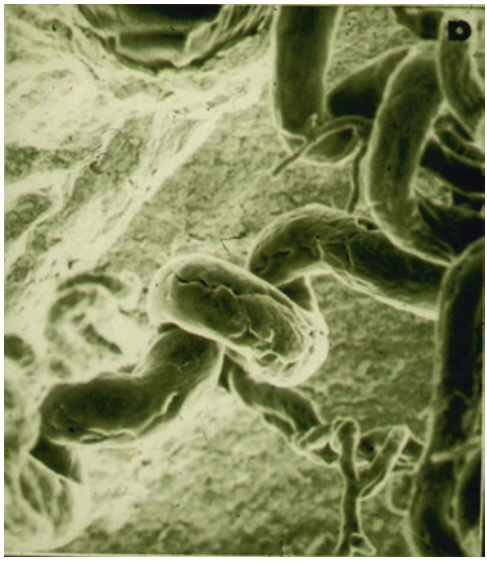

Fig. 9 Scanning electron microscopy: spiral arterioles on day 23

cytoplasmic organelles are poorly developed and randomly distributed, with occasional cytoplasmic vacuoles, and short blunt microvilli are noted on the apical border of the cells [11]. The stroma is dense with a network of precollagen fibers surrounding spindle-shaped cells, with an occasional lymphoid cell infiltrate. Perimenopausal irregular vaginal bleeding is common, and endometrial biopsies may show glandular crowding due to stromal breakdown. The crowding and back-

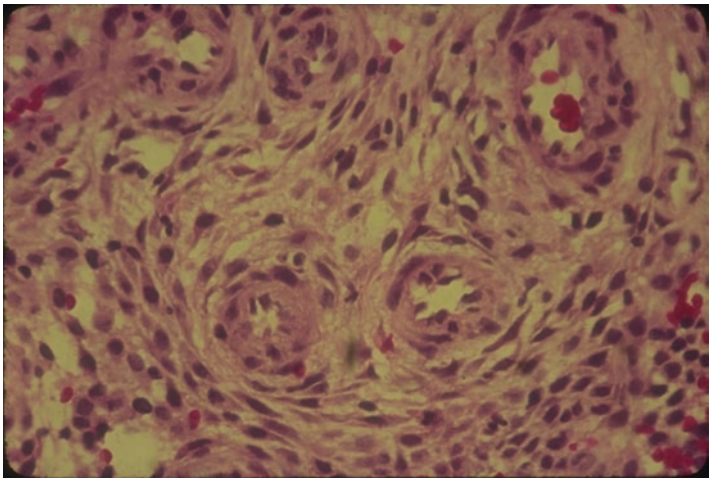

Fig. 10 Spiral arteriole surrounded by decidualized stromal cells, day 24, H&E x 100

to-back glandular pattern may arise suspicions of hyperplasia and neoplasia. Careful examination of the epithelial cells to identify nuclear atypia (different from "smudged" nuclei), special stains for p53, K67, and estrogen/progesterone receptors are helpful for the diagnosis and further management of the patient, including hormone therapy for menopause. Extragonadal estrogen in postmenopausal women is derived from androgen conversion to estrogen. Available estrogen varies with the substrate; as the amount of fat and the aromatase capacity of fat tissue increase, circulating levels of total and free estrone and estradiol increase [12–15]. With obesity sex hormone-binding globulin levels decrease providing greater androgen substrate availability and higher concentration of free biologically active estrogens [16–19].

Endometrial biopsies are frequently performed on peri- and postmenopausal women, in order to establish the nature of often occurring irregular vaginal bleeding, to rule out possible malignancy or precursor of malignant changes, and to establish a baseline before hormone replacement therapy (HRT) is recommended. The interpretation of the histologic findings may be difficult as hormonal influences are often unpredictable during the process of ovarian gradual failure, and locally, the hormone receptors may be irregularly distributed or absent. Given the wide variety of histopathologic and immunopathologic patterns, the management of the patient, hormone therapy including HRT, has to be individualized and coordinated with the general state of health and metabolism (especially obesity and diabetes) and correlated with the baseline endometrial biopsy.

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