Histology of the Female reproductive system (part 3)

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Cervix

It is the lower, cylindrical part of the uterus. It differs histologically from the rest of the uterus.

The **endocervix** lies around the internal os towards the uterine cavity, it is covered with endocervical mucosa simple columnar epithelium with a thick lamina propria, with many large, branched, mucus-secreting cervical glands. There is no spiral arteries and there is no cyclical changes of its epithelium during ovarian cycle nor shedding during menstruation, however its secretion changes during various stages of the menstrual cycle. Deeper, the cervical wall is primarily fibromuscular tissue

Near the time of ovulation and under estrogen effect cervical glands secrete abundant serous fluid that facilitate the entry of spermatozoa into uterine cavity.

After ovulation and under progesterone effect, cervical glands undergo proliferation and produce thick viscous mucous secretion (plug) that prevents entry of further sperms. Likewise, during pregnancy to prevent ascending of pathogenic microorganisms into uterine cavity.

The **exocervix** lies around the external os as it projects into the upper vagina and it is covered by exocervical mucosa that is nonkeratinized stratified squamous epithelium continuous with that of the vagina. The junction between this squamous epithelium and the mucus-secreting columnar epithelium of the endocervix occurs in the **transformation zone**, an area just outside the external os that shifts slightly with the cyclical changes in uterine size. Repeated exposure of the transformation zone to the vaginal environment can stimulate metaplasia and lead to dysplasia and consequent cervical cancer at the site.

*The incidence of cervical cancer has been greatly reduced by widespread routine screening test. Using exfoliative cervical cells to examine for cellular changes in the epithelial cells. This test called **Pap smear** that uses cells scraped from cervix to be examined. Abnormal cells suggestive of precancerous changes can be diagnosed early. The human papilloma virus (HPV) is strong risk factor for cervical cancer, therefore a vaccine has been developed to reduce the occurrence of cancer.*

*Prior to parturition (birth), the cervix undergoes remodeling of its connective tissue and extensive loss of collagen, as a result the cervix softens, the cervical canal dilates and birth occurs easily. This process called **cervical effacement**.*

Vagina

The wall of the vagina lacks glands and consists of a mucosa, a muscular layer and an adventitia. The epithelium of the vaginal mucosa is nonkeratinized stratified squamous epithelium, which is stimulated by estrogen to synthesize and accumulate glycogen. When these cells desquamate (shed), normal flora (the good bacteria) metabolize glycogen to lactic acid causing acidic low pH within the vagina, which helps protect against pathogenic microorganisms. The lamina propria is rich with elastic fibers with numerous papillae projecting into epithelium. The mucosa normally contains lymphocytes and neutrophils in large quantities.

There is no mucous glands in the wall of the vagina, however, mucus in the vagina is produced by the cervical glands and during sexual arousal mucous is also provided by paired greater vestibular glands (of Bartholin).

External genitalia

The female external genitalia or vulva, consist of clitoris, labia minora, labia majora, and some glands that open into the vestibulum.

The urethra and the ducts of the vestibular glands open into the vestibulum (space enclosed by the labia minora). The two major vestibular glands or glands of Bartholin are situated on either side of the vestibulum. Numerous minor vestibular glands are scattered.

- The clitoris and the penis are homologous in embryonic origin and histological structure.
- The labia minora are folds of skin with a core of spongy connective tissue permeated by elastic fibers.
- The labia majora are folds of skin that is homologous and histologically similar to the skin of the scrotum.

The external genitalia are abundantly supplied with sensory tactile nerve endings, including Meissner's and Pacinian corpuscles, which contribute to the physiology of sexual arousal.

Mammary gland

Breasts develop as downgrowths from the epidermis along a line (milk line or streak) which runs obliquely from the axilla toward the groin on each side. In humans normally only one breast develops on each side, but occasionally an accessory breast develops.

Each mammary gland consists of 15-25 lobes of the compound tubuloalveolar type whose function is to secrete nutritive milk for newborns. Each lobe, separated from the others by dense connective tissue septa with much adipose tissue, and considered as a separate gland with its own excretory lactiferous duct. Lactiferous ducts, each 2-4.5 cm ling, emerge independently in the nipple with 15-25 openings. The histologic structure of the mammary glands varies according to sex, age, and physiologic status.

Breast development during Puberty

Before puberty, mammary gland is composed of only lactiferous sinuses near the nipple, with very small branching ducts emerging from the sinuses.

At puberty, increased levels of estrogens cause the breast to grow as a result of adipocyte accumulation and elongation of the duct system.

In nonpregnant adult women each mammary gland lobe consists of many lobules (AKA **terminal duct lobular units TDLU**). Each lobule has several small, branching ducts called intralobular ducts, but the attached secretory units are small and rudimentary.

Lactiferous sinuses are lined with stratified cuboidal epithelium, and the lining of the lactiferous ducts and terminal ducts is simple cuboidal epithelium with many myoepithelial cells, sparse fibers of smooth muscle also encircle the larger ducts. Intralobular ducts are embedded in loose, vascular connective tissue called intralobular connective tissue. A denser less cellular interlobular connective tissue separates lobules.

In the premenstrual phase, connective tissue of the breast becomes edematous, making the breasts slightly larger under the effect of progesterone.

The **areola** is the skin surrounding the nipple, contains sebaceous glands called (areolar glands of Montgomery) that secrete an oily substance that helps lubricate the skin, as well as rich sensory nerve as tactile receptors that are continues with mucosa of the lactiferous sinuses. The areola contains more melanin than elsewhere, it darkens further during pregnancy.

The **nipple** is composed of dense connective tissue rich in smooth muscle fibers that run parallel to the lactiferous sinuses and produce nipple erection when contracted.

Breast during Pregnancy and Lactation

The mammary glands undergo growth during pregnancy under synergistic effect of several hormones (estrogen, progesterone, prolactin and the placental lactogen):

- Cell proliferation in the secretory alveoli at the ends of intralobular ducts. The alveoli are composed of cuboidal epithelium, with stellate myoepithelial cells between the secretory cells and basal lamina.
- Further growth and branching of ductal system.
- The stroma become less prominent due to growth TDLU tissue.
- Intralobular loose connective tissue is infiltrated with lymphocytes and plasma cells (plasma cells become more numerous in late pregnancy).

During late pregnancy the glandular alveoli and ducts are filled and dilated by accumulation of **colostrum** (a fluid rich in proteins and leukocytes, which is produced under the effect of prolactin. Immunoglobulin A (IgA) antibodies are produced by plasma cells and transferred into colostrum to provide passive immunity for the fed newborn.

Following parturition (birth), the alveoli start active milk production (lactation) and become filled and extensively dilated with milk (stimulated mainly by prolactin). Epithelial cells of the secretory alveoli rnlarge in size and activate secretory processes of lactation:

- Large amounts of proteins (caseins, β-lactoglobulin and α-lactalbumin) are synthesized in a merocrine manner.
- Lipid droplets in form of short and long-chain fatty acids and cholesterol undergo apocrine secretion.
- Lactose, the main milk carbohydrate and energy source and considered the major constituent of milk.

Milk ejection reflex; is a reflex arc that is initiated with stimulation of tactile nerve endings in the nipple and areola to send a stimulus to hypothalamus triggering a release of oxytocin (as well as prolactin) to stimulate myoepithelial cells contraction and release of produced milk into lactiferous ducts and sinuses and into the newborn mouth.

Post-lactational Regression in the Mammary Glands

With stopping of breastfeeding (weaning), the majority of alveoli that developed during pregnancy and after delivery degenerate with their epithelial cells undergo apoptosis and autophagy. The ductal system returns to its previous state of inactivity.

After menopause, both alveoli and ducts are reduced further in size with loss of fibroblast, collagen and elastic fibers in stroma.

Breast cancer is usually derived from terminal lobules of the gland (the most common is invasive ductal carcinoma). It is the most common cancer among adult female population. It's late diagnosis lately could result in poor prognosis, local invasion to adjacent structures, metastasis to axillary lymph nodes or via blood vessels to critical organs such as brain, lungs, liver or others. However, if diagnosed early (through self-examination, mammography and other modalities) and early treatment could result in better prognosis (better outcome, better health and reduced mortality rate).

In vitro fertilization (IVF)

The selected women for IVF undergo hyperstimulation of the ovaries by gonadotropins and clomiphene with or without FSH to induce multiple follicle development and maturation. Mature pre-ovulatory oocytes are collected from Graafian follicles by either laparoscope or ultrasound guided percutaneous aspiration or trans-vaginal aspiration. These oocytes incubated in special medium. The collected semen is placed in special medium, then, the collected oocytes are added to the medium containing the collected semen. 12-16 hours later, the oocytes are examined to determine the presence of male and female pronuclei (the indication of successful fertilization). At this stage, the fertilized oocyte is transferred into special medium for 24-48 hours to allow it to grow into the stage of 4-6 cells. After that, the embryos are transferred into the uterus which is already prepared by appropriate hormonal treatment to receive the embryos. After transferring the embryos, intensive progesterone treatment is usually begun to mimic the function of corpus luteum of pregnancy.