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DEPARTMENT:NURSING

1. Briefly discuss the cyclic changes in any two of the following

(a) cervix (b) vagina (c) breast

CERVIX

The **vaginal epithelium** is the inner lining of the vagina consisting of multiple layers of (squamous) cells. The basal membrane provides the support for the first layer of the epithelium- the basal layer. The intermediate layers lie upon the basal layer and the superficial layer is the outermost layer of the epithelium. Anatomists have described the epithelium as consisting of as many as 40 distinct layers. The mucus found on the epithelium is secreted by the cervix and uterus. The rugae of the epithelium create an involuted surface and result in a large surface area that covers 360 cm^3. This large surface area allows the trans-epithelial absorption of some medications via the vaginal route.

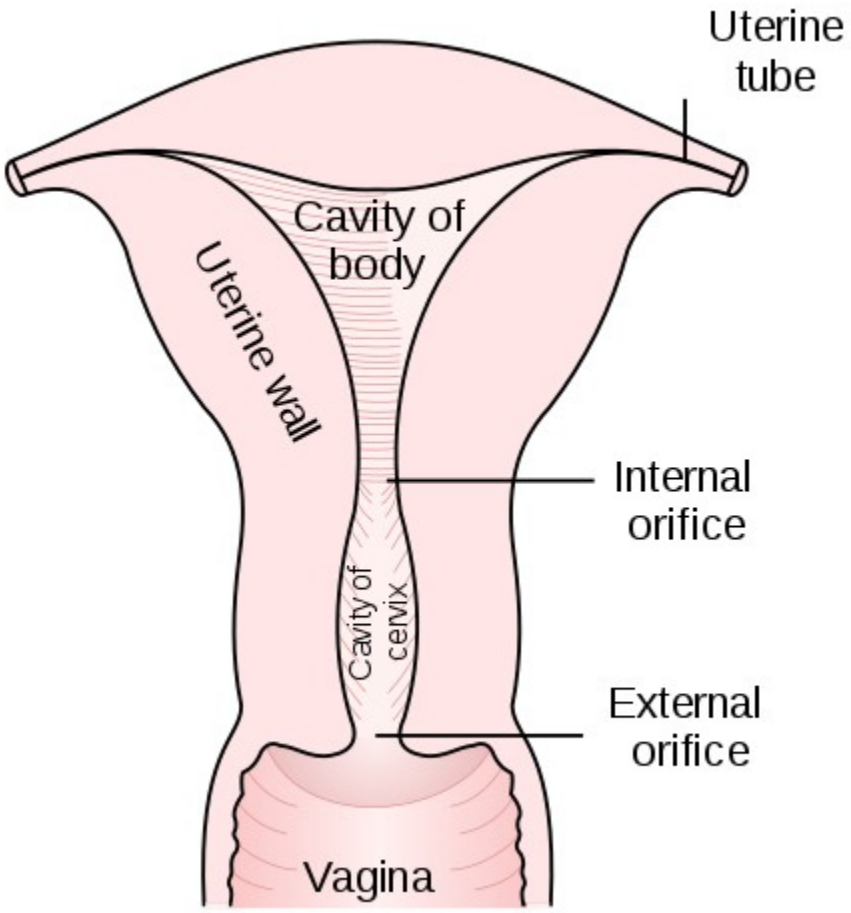
In the course of the reproductive cycle, the vaginal epithelium is subject to normal, cyclic changes, that are influenced by estrogen: with increasing circulating levels of the hormone, there is proliferation of epithelial cells along with an increase in the number of cell layers. As cells proliferate and mature, they undergo partial cornification. Although hormone induced changes occur in the other tissues and organs of the female reproductive system, the vaginal epithelium is more sensitive and its structure is an indicator of estrogen levels. Some Langerhans cells and melanocytes are also present in the epithelium. The epithelium of the ectocervix is contiguous with that of the vagina, possessing the same properties and function. The vaginal epithelium is divided into layers of cells, including the basal cells, the parabasal cells, the superficial squamous flat cells, and the intermediate cells. The superficial cells exfoliate continuously and basal cells replace the superficial cells that die and slough off from the stratum corneum. Under the stratus corneum is the stratum granulosum and stratum spinosum. The cells of the vaginal epithelium retain a usually high level of glycogen compared to other epithelial tissue in the body. The surface patterns on the cells themselves are circular and arranged in longitudinal rows. The epithelial cells of the uterus possess some of the same characteristics of the vaginal epithelium. Studies in nonhuman primates indicate that changes in the thickness and integrity of the vaginal epithelium affect the transmission rates of HIV-1, but few studies have examined the normal variations that may occur in the vagina of normal macaques as a result of aging or changes in the menstrual cycle. This study was conducted to determine if differences occur in the thickness of the vaginal mucosa with age or menses. Vaginal mucosal thickness was compared in 46 rhesus macaques grouped as juvenile (1-3 years old), mature cycling (3-21 years old), and geriatric (> 21 years old). Epithelia of mature cycling macaques were also compared at different stages of the menstrual cycle. Older females (> 21 years) had the thinnest and least keratinized epithelium of all groups, followed by the youngest females (< 3 years). The vaginal epithelium was also thinner in cycling macaques during menses compared to the follicular stage. In addition, young, geriatric, or cycling macaques during menses had minimal keratinization. We hypothesize that normal physiologic changes in the vaginal epithelium of women occur with age and menses, which may affect a woman's susceptibility to HIV-1 transmission and other sexually transmitted diseases. Also, age and menstrual cycle should be considered when designing vaginal transmission experiments in rhesus macaques.

Assessment of changes in cycling macaques at different stages of the menstrual cycle

To evaluate the changes in vaginal epithelium during the normal menstrual cycle, vaginal epithelium from six normal, healthy, cycling female rhesus macaques between 5.8 and 10 years of age were examined. These animals were also born and raised in outdoor breeding corrals at the TNPRC until they were assigned to this study, at which time they were transferred indoors and individually cage-housed in a biosafety level 2 research facilities in accordance with the standards of the American Association for Accreditation of Laboratory Animal Care. Animals were acclimated to their cages for 3–6 months before testing procedures began. To assess the stage of the menstrual cycle, macaques were first placed on a menses watch (observations began in mid-June) in which they were observed daily to detect the first day of vaginal blood, signaling the onset of menses (day 0 of the menstrual cycle). Since the average cycle in macaques is 28 days, the vaginal mucosa was biopsied exactly 14 days later and these samples were used to represent 'follicular' stage biopsies. From day 0, the vaginal mucosa was again biopsied exactly 28 days later for luteal-phase samples. Beginning on day 14 (peak follicular phase), macaques were briefly sedated with 10 mg/kg i.m. ketamine (Fort Dodge Animal Health, Fort Dodge, IA, USA) and sera was collected every third day for 35 days subsequently to assess hormone profiles and confirm these cyclic stages by estrogen and progesterone levels (see below). In all cases, vaginal biopsies were collected from macaques anesthetized with Telazol (8 mg/kg i.m.; Fort Dodge Animal Health) using 3 mm biopsy forceps. For these procedures, anesthetized macaques were placed in modified ventral recumbency with their hips slightly elevated and ventral a full thickness mucosal biopsy of vaginal epithelium that included the surface to the basal epithelial

The cervix is also called the cervix uteri. It is the lower part of the uterus in the human female reproductive system. The cervix is usually 2 to 3 cm long (~1 inch) and roughly cylindrical in shape, which changes during pregnancy. The narrow,central cervical canal runs along its entire length, connecting the uterine cavity and the lumen of the vagina.

Diagram of the Uterus and part of the vagina.
Cyclic changes of the cervix throughout a month



Every woman has a different ‘normal’, but certain changes in the cervix throughout the month indicate when a person may be ovulating. Alongside the Basal Body Temperature (BBT), Cervical Mucous (CM) and tracking the person’s menstrual cycle, notes on cervical changes should be integral to the person’s fertility diary. When a person starts her period (Day One of her cycle), there’s no need to feel the cervix for changes, as the person is clearly menstruating. Once the bleeding stops, she may have a few days (possibly up to a week) as a ‘pre-fertile’ phase. This is the time from when the bleeding finishes and when the fertile phase begins. During the pre-fertile phase, the lining of the uterus starts to thicken, regenerating after the period has finished. At the same time, a group of eggs in the ovaries start to ripen. Fertile ground After your pre-fertile phase, the person moves into the fertile phase of the cycle, which is when she really want to start noting any changes in the cervix, particularly if the person is having trouble tracking the cervical mucous (CM).As oestrogen levels increase, a woman's uterus and cervix start to produce a special fertile mucous which is capable of protecting the man's sperm and helping them survive for up to three to five days in the woman's body. The fertile mucus sits in the opening of the woman's cervix and lines her uterus and fallopian tubes. The mucus acts as a continuous stream to transport sperm up into a woman's fallopian tubes, in readiness for when an egg is released. Once the woman releases an egg (orovulates) it only survives for around 12 to 24 hours. The fertile phase is also called the follicular or proliferative stages, as the egg is still maturing and the lining of the uterus continues to thicken. A woman's fertile phase usually starts about three to five days before ovulation, until

the egg is released. If a person feels her cervix it should be higher, softer, wetter and slightly more open when compared to the previous days.
During ovulation, the cervix will now be at it highest point and may even be difficult to reach. It should feel very wet, soft and open. After ovulation. The time after ovulation is the post-fertile phase of the menstrual cycle. The post-fertile phase lasts for about 14 days(ranging from12 to 16 days) until the bleeding starts again. The medical terms for this phase are the ‘Luteal phase’ – which refers to the capsule left in the ovary that encased the released
egg called the 'Corpus Luteum' (or 'white body'). The corpusluteum produces the progesterone hormone, bringing the lining of the uterus (or 'endometrium') to maturity. Or the alternative, the 'Secretory phase', because the lining of the uterus is now able to secrete glucose, aimed at feeding a developing baby until they fully implant in the lining of the uterus and start to draw on their mother for nourishment. At this time, the cervix should feel quite similar to the pre-fertile
phase: lower, firmer, only slightly moist or even dry and tightly closed again layer was collected from the lateral vaginal wall.

BREAST

The ultrastructure of resisting human female mammary gland epithelium was studied in 21 females of reproductive age (15–36 years) with regular menstrual cycles. Grossly and light microscopically normal appearing breast tissue contiguous to benign lesions was selected and processed at the time of frozen section diagnosis. Acino-ductular epithelium was ultrastructurally classifiable into two major categories: Phase I—non-secretory, and Phase II—potentially secretory. The above cells were often further classifiable into Phase IA cells, whose main feature was prominent intracellular fluid retention, and Phase IIA epithelium, characterized by cytoplasmic glycogen deposits. The preovulatory phase of the menstrual cycle was associated with a peak number of Phase I cells, while in the postovulatory phase there was a preponderance of Phase II cells. In the late preovulatory phase, Phase IA cells, and in the early postovulatory phase, Phase IIA cells were more commonly found. The relationship between the menstrual stage and cyclic changes in the ultrastructural morphology of mammary gland epithelium presumably represents the effects of ovarian steroid activity on the cellular physiology of an endocrine-sensitive end organ; this is a cell biological phenomenon parallel to the better known cyclic cellular alterations occurring in the endometrium during the normal menstrual cycle. An understanding of the cyclic ultrastructural changes of mammary gland epithelium may lay the basis for a sounder and more meaningful interpretation of breast pathology and its pathogenesis.

The volumes and spin-lattice (T_1) relaxation times of breast tissues and parenchymal water content were measured non-invasively by magnetic resonance imaging (MRI) in eight healthy women during four to eight consecutive menstrual cycles. Total breast volume, and parenchymal volume, T_1 relaxation time and water content were lowest between days 6 and 15. Between days 16 and 28, parenchymal volume, T_1 relaxation time and water content rose sharply by 38·9%, 15·1% and 24·5%, respectively, and peaked after day 25. Within 5 days of the onset of menses, parenchymal volume fell sharply by 30·3%, while water content declined by 17·5%. Rising parenchymal volume in the second half of the menstrual cycle is not solely due to increased tissue water content and provides in vivo evidence for both growth and increased tissue fluid at this time.

2.)explicate any one of the following

a. menstrual cycle

b. hormonal regulation of the menstrual cycle

MENSTRUAL CYCLE

Menstruation occurs on a **monthly cycle** throughout female reproductive life. **Menarche** (the first menstrual cycle) normally occurs between the ages of 11 and 15 and the menopause between the ages of 45 and 55. The normal duration of a single cycle is **21-35 days**. In this article we will focus on the reproductive hormones, the ovarian cycle and the uterine cycle.

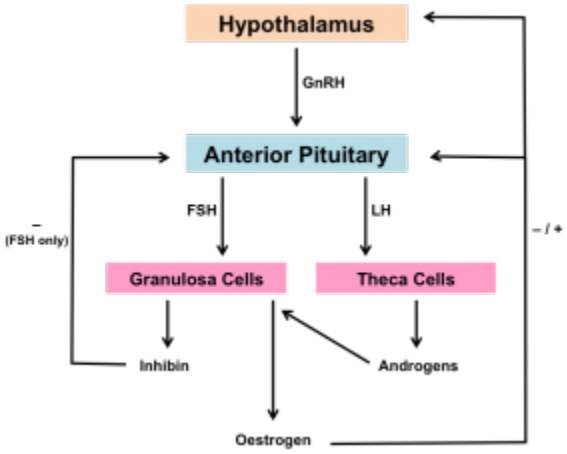
The Hypothalamic-Pituitary-Gonadal (HPG) Axis

The hypothalamus, anterior pituitary gland and gonads (ovaries) work together to regulate the menstrual cycle. Gonadotropin releasing hormone (**GnRH**) from the hypothalamus stimulates luteinising hormone (LH) and follicular stimulating hormone (FSH) release from the anterior pituitary gland. LH and FSH are gonadotropins that act primarily on the ovaries in the female reproductive tract:

- **FSH** binds to granulosa cells to stimulate follicle growth, permit the conversion of androgens (from theca cells) to oestrogens and stimulate inhibin secretion
- **LH** acts on theca cells to stimulate production and secretion of androgens

The menstrual cycle is controlled by feedback systems:

- Moderate **oestrogen** levels: negative feedback on the HPG axis
- High oestrogen levels (in the absence of progesterone): positively feedback on the HPG axis
- Oestrogen in the presence of **progesterone**: negative feedback on the HPG axis
- **Inhibin**: selectively inhibits FSH at the anterior pituitary



The Ovarian Cycle

Follicular Phase

The **follicular phase** marks the beginning of a new cycle as follicles (oocytes surrounded by stromal cells) begin to mature and prepare to release an oocyte.

At the start of a new cycle (menses) there is little ovarian hormone production and the follicle begins to develop independently of gonadotropins or ovarian steroids. Due to the low steroid and inhibin levels, there is little **negative feedback** at the HPG axis resulting in an increase in FSH and LH levels. These stimulate follicle growth and oestrogen production.

Only one dominant follicle can continue to maturity and complete each menstrual cycle. As oestrogen levels rise, negative feedback reduces FSH levels, and only one follicle can survive, with the other follicles forming **polar bodies**.

Follicular oestrogen eventually becomes high enough to initiate positive feedback at the HPG axis, increasing levels of GnRH and gonadotropins. However, the effect is only reflected in LH levels (the **LH surge**) due to the increased follicular inhibin, selectively inhibiting FSH production at the anterior pituitary. Granulosa cells become luteinised and express receptors for LH.

Ovulation

In response to the **LH surge**, the follicle ruptures and the mature oocyte is assisted to the fallopian tube by fimbria. Here it remains viable for fertilisation for around 24 hours.

Following ovulation, the follicle remains luteinised, secreting oestrogen and now also **progesterone**, reverting back to negative feedback on the HPG axis. This, together with inhibin (inhibits FSH) stalls the cycle in anticipation of fertilisation.

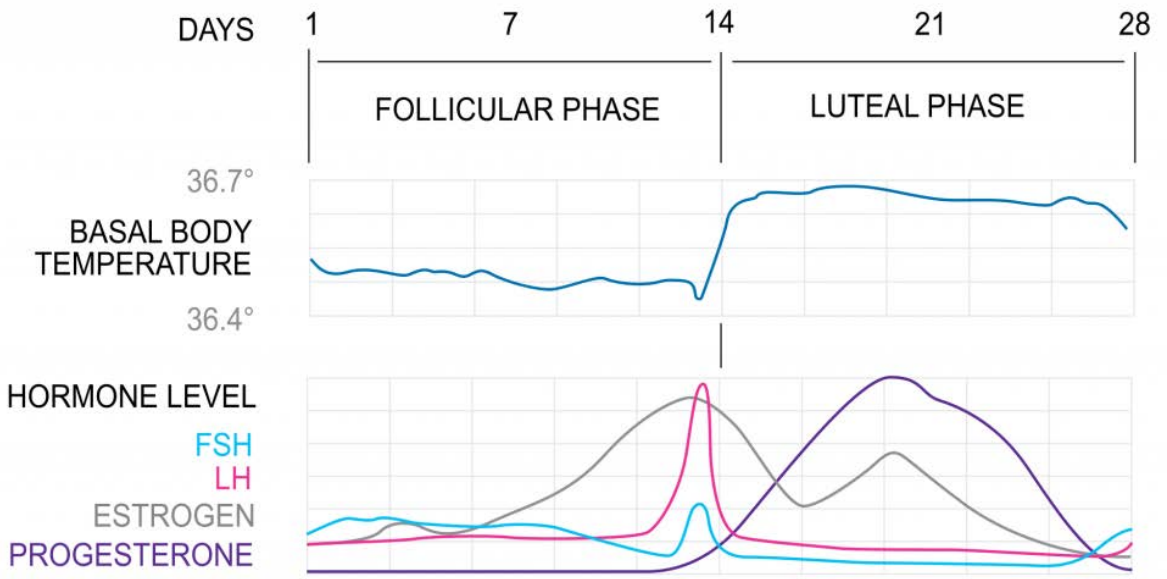
Luteal Phase

The **corpus luteum** is the tissue in the ovary that forms at the site of a ruptured follicle following ovulation. It produces oestrogens, progesterone and inhibin to maintain conditions for fertilisation and implantation.

At the end of the cycle, in the absence of fertilisation, the corpus luteum **spontaneously regresses** after 14 days. There is a significant fall in hormones, relieving negative feedback, resetting the HPG axis ready to begin the cycle again.

If fertilisation occurs, the syncytiotrophoblast of the embryo produces human chorionic gonadotropin **(HcG),** exerting a luteinising effect, maintaining the corpus luteum. It is supported by placental HcG and it produces hormones to support the pregnancy. At around 4 months of

gestation, the placenta is capable of production of sufficient steroid hormone to control the HPG axis.



The Uterine Cycle

Proliferative Phase

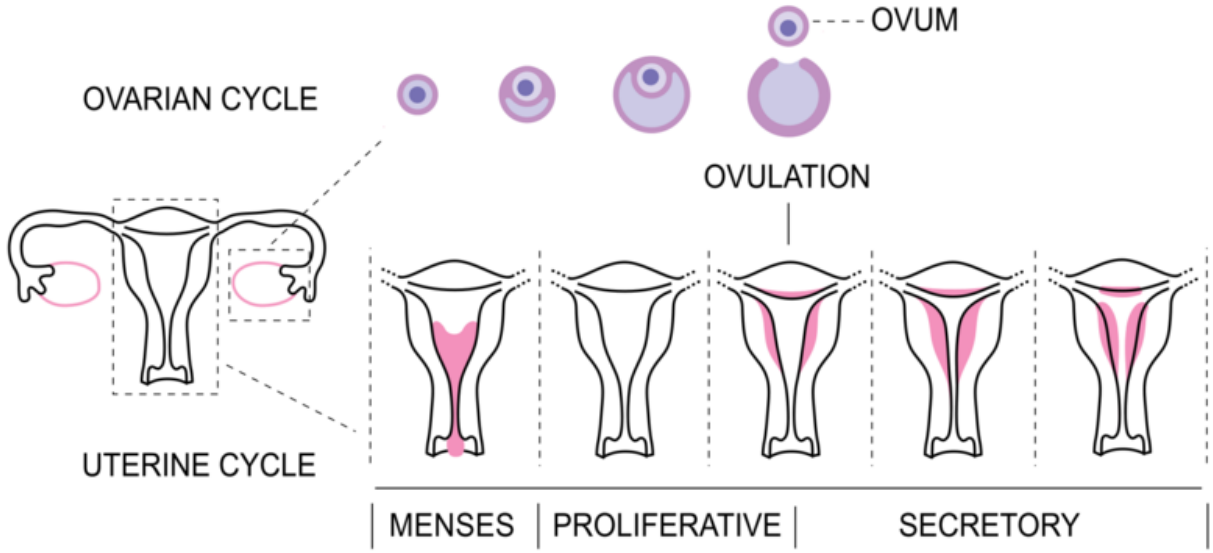
Following menses, the **proliferative phase** runs alongside the follicular phase, preparing the reproductive tract for fertilisation and implantation. **Oestrogen** initiates fallopian tube formation, thickening of the endometrium, increased growth and motility of the myometrium and production of a thin alkaline cervical mucus (to facilitate sperm transport).

Secretory Phase

The secretory p**hase** runs alongside the luteal phase. Progesterone stimulates further thickening of the endometrium into a glandular secretory form, further thickening of the myometrium, reduction of motility of the **myometrium,** thick acidic cervical mucus production (a hostile environment to prevent polyspermy), changes in mammary tissue and other metabolic changes.

Menses

Menses marks the beginning of a new menstrual cycle. It occurs in the absence of fertilisation once the corpus luteum has broken down and the internal lining of the uterus is shed. Menstrual bleeding usually lasts between 2-7 days with 10-80ml blood loss.



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