

ENDOCRINE CONTROL OF THE OESTROUS CYCLE



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ESTRUS CYCLE

The **estrous cycle** (British spelling, **oestrous**) is the main reproductive cycle of species females of non-primate mammals, for example *rats, mice, horses, pig, dogs, sheep, goats, cows, buffaloes* etc. Estrous cycles are characterized by morphological changes in ovaries, the uterus and the vagina. Estrous cycle is the reproductive system in most mammals except most primates (including human). In those animals reproductive hormones cause the cycles to start after puberty in sexually mature females. *The mean duration of the estrous cycle was 4-5 days for most of **female rats** and it may vary in others.*

The estrus cycle consists of *four phases*, namely **proestrus**, **estrus**, **metestrus** and **diestrus**. During this period, the vaginal mucosa undergoes tremendous structural changes and is affected by hormones such as **FSH** (stimulates the growth and development of ovarian follicles), **LH** (regulates estrogen and progesterone hormones), **progesterone** and **estradiol**.

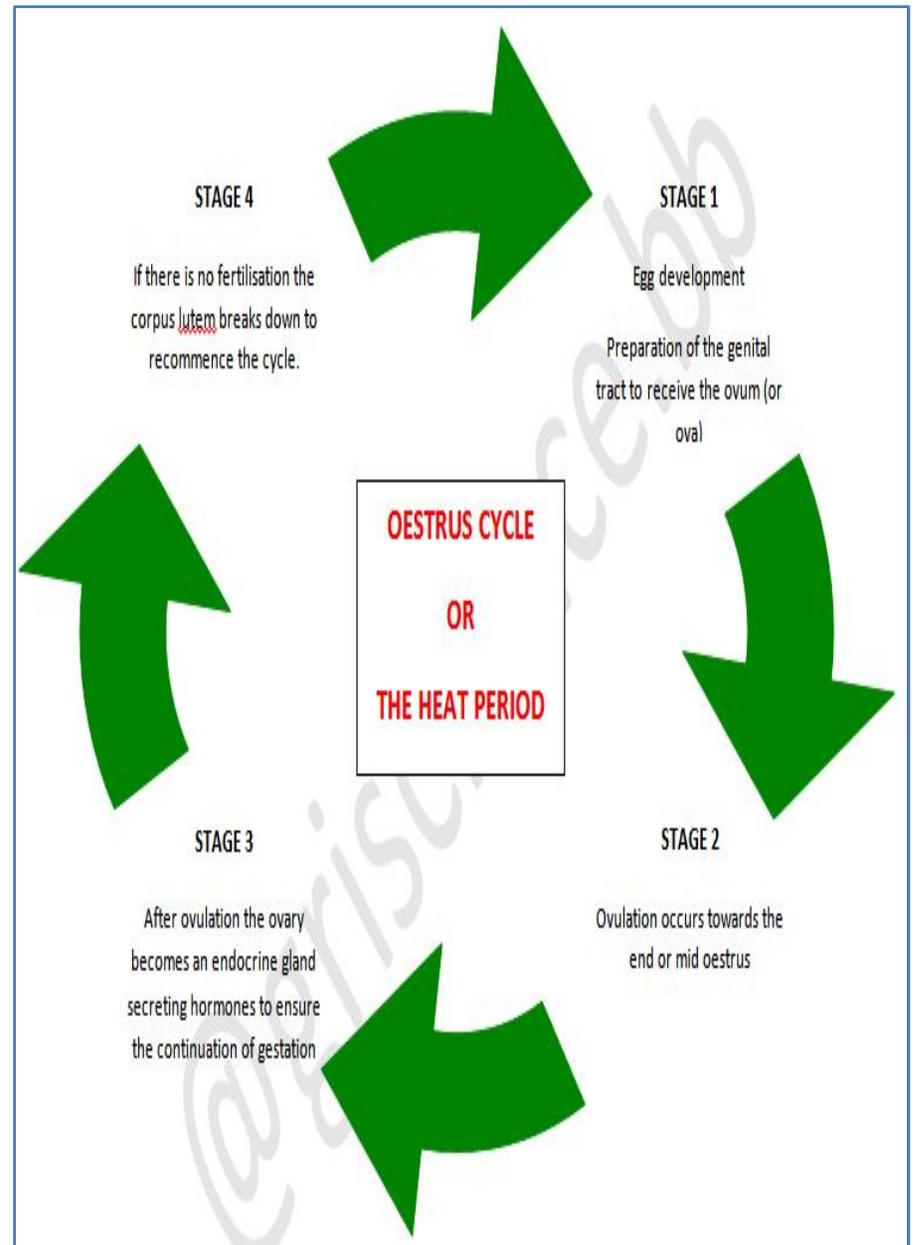
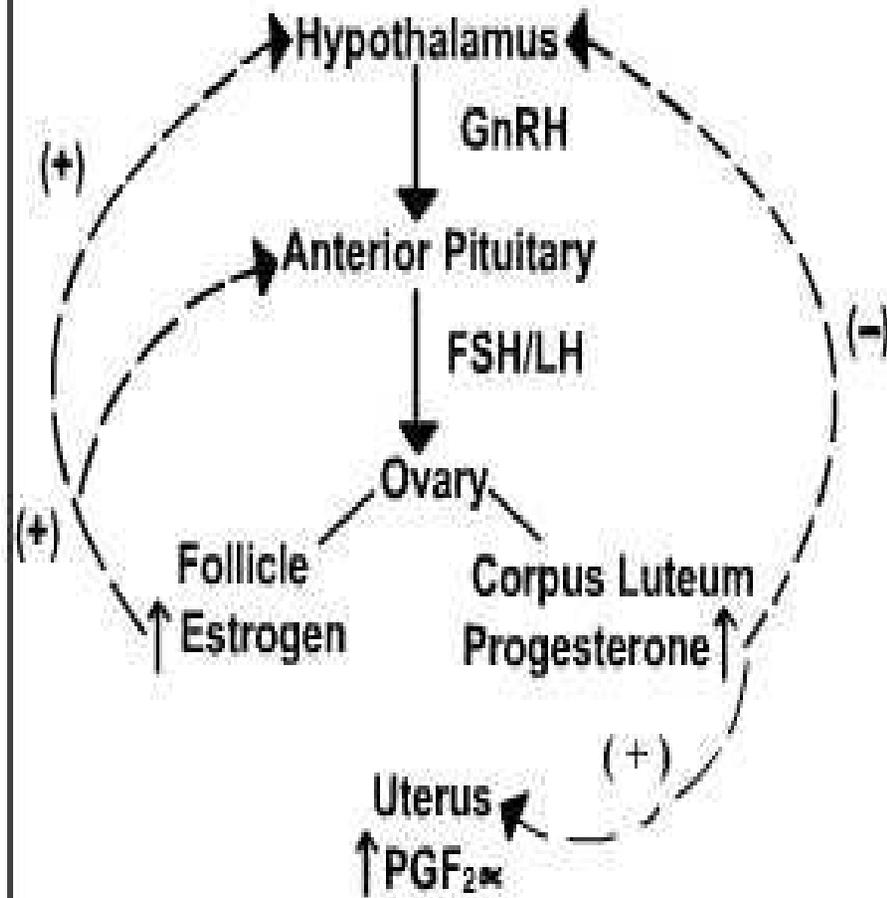
ESTRUS CYCLE & ITS ENDOCRINE CONTROL

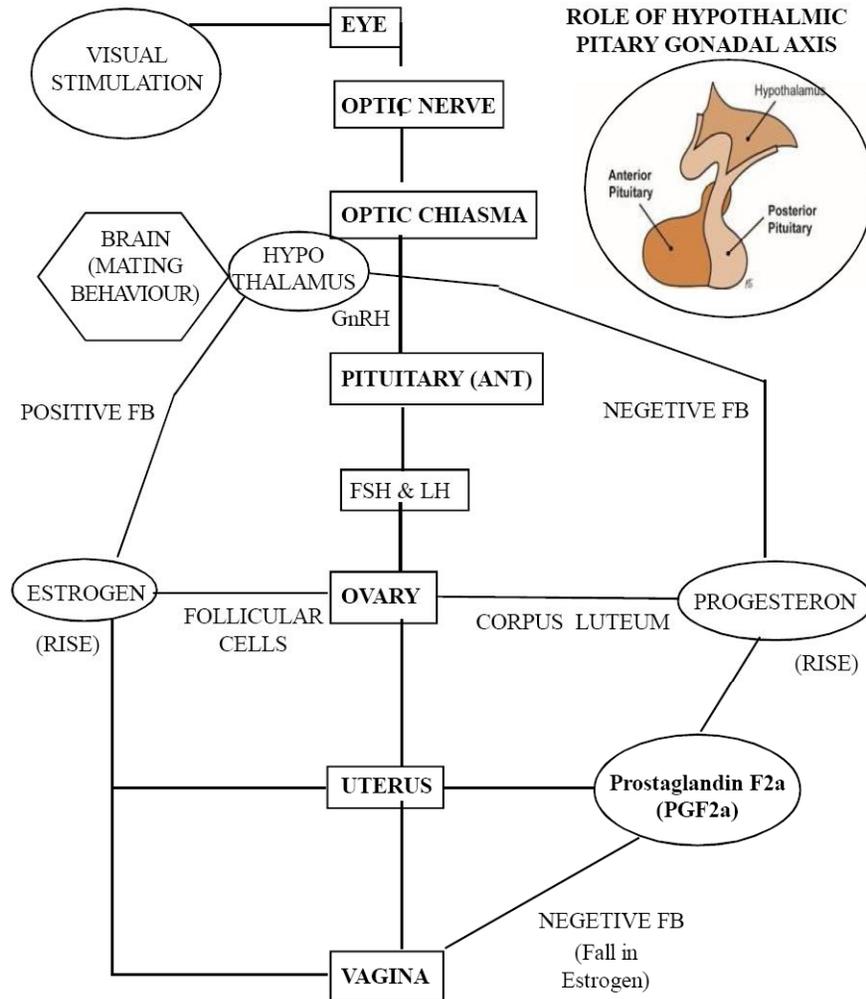
Introduction

The cyclical changes that occur in the female reproductive tract of non-primate mammals are initiated and regulated by the **hypothalamic-pituitary-ovarian (HPO) axis**. Although folliculogenesis occurs independently of hormonal stimulation up until the formation of early tertiary follicles, the gonadotrophins, i.e. luteinising hormone (LH) and follicle stimulating hormone (FSH) are essential for the completion of follicular maturation and development of mature preovulatory (Graafian) follicles.

Pituitary release of gonadotrophins, thus drives follicular maturation and secretion of oestrogen during prooestrus. Levels of LH and FSH begin to increase just after dioestrus. Both hormones are secreted by the same secretory cells (gonadotrophs) in the ***pars distalis*** of the anterior pituitary (***adenohypophysis***). FSH stimulates development of the zona granulosa and triggers expression of *LH receptors* by granulosa cells. LH initiates the synthesis and secretion of **androstenedione** and, to a lesser extent, *testosterone* by the theca interna; these androgens are utilised by granulosa cells as substrates in the synthesis of **oestrogen**.

HYPOTHALAMIC-PITUITARY GONADAL AXIS

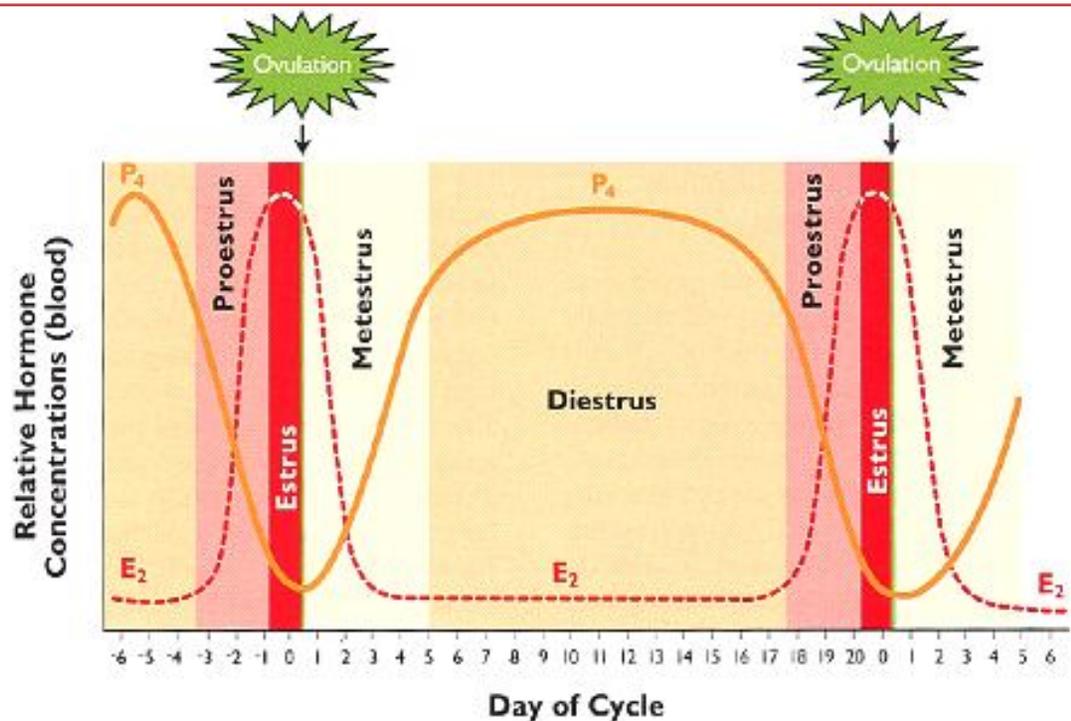




In domestic mammals and also in rats, **PGF2alpha** is produced by the uterus when stimulated by oxytocin, in the event that there has been no implantation during the luteal phase. It acts on the corpus luteum to cause luteolysis, forming a corpus albicans and stopping the production of progesterone.

**HORMONAL REACTION (=EFFECT OF ESTROGEN & PROGESTERON)
BEFORE & AFTER MATING**

1 Diestrus between 2 Estruses and Hormone levels (E2 & P4)

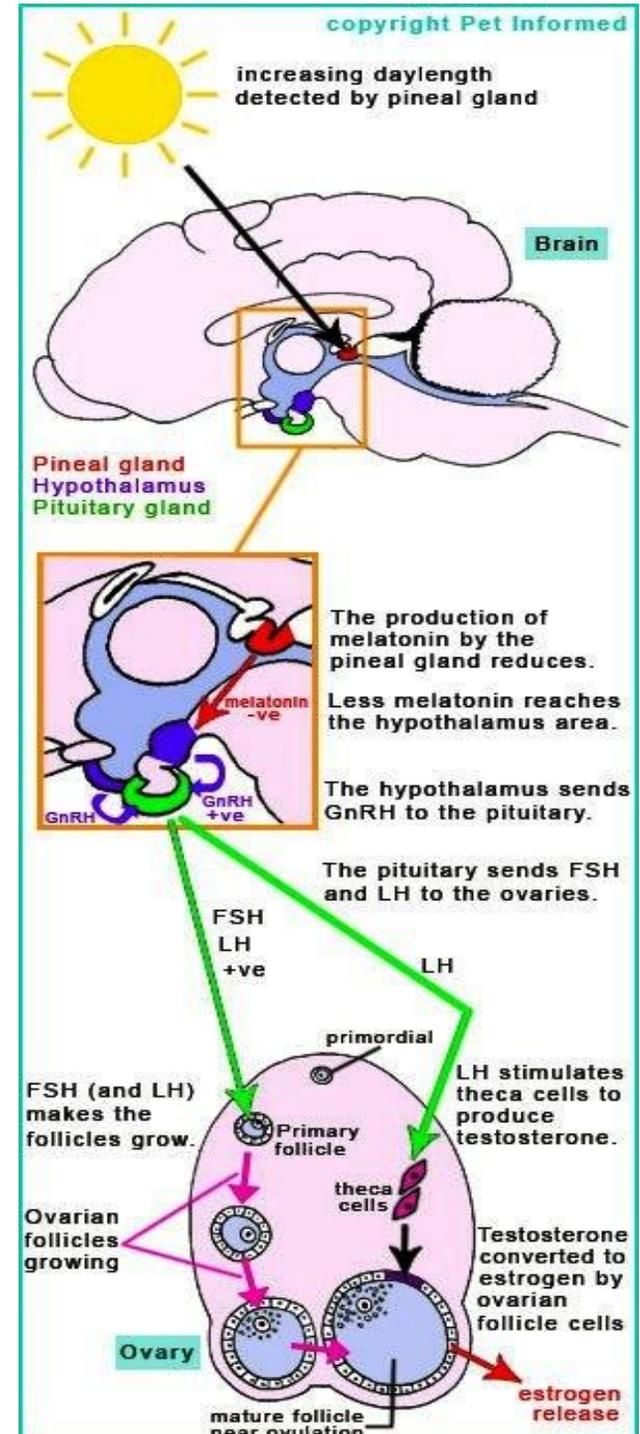


Proestrus is characterized by a significant rise in E₂ produced by developing follicles

When estradiol rises a certain level, the female enters behaviour estrus and then ovulates.

Following ovulation, cells of the follicle are transformed into luteal cells that form the corpus luteum (CL) during metestrus.

Diestrus is characterised by a fully functional CL and high progesteron.



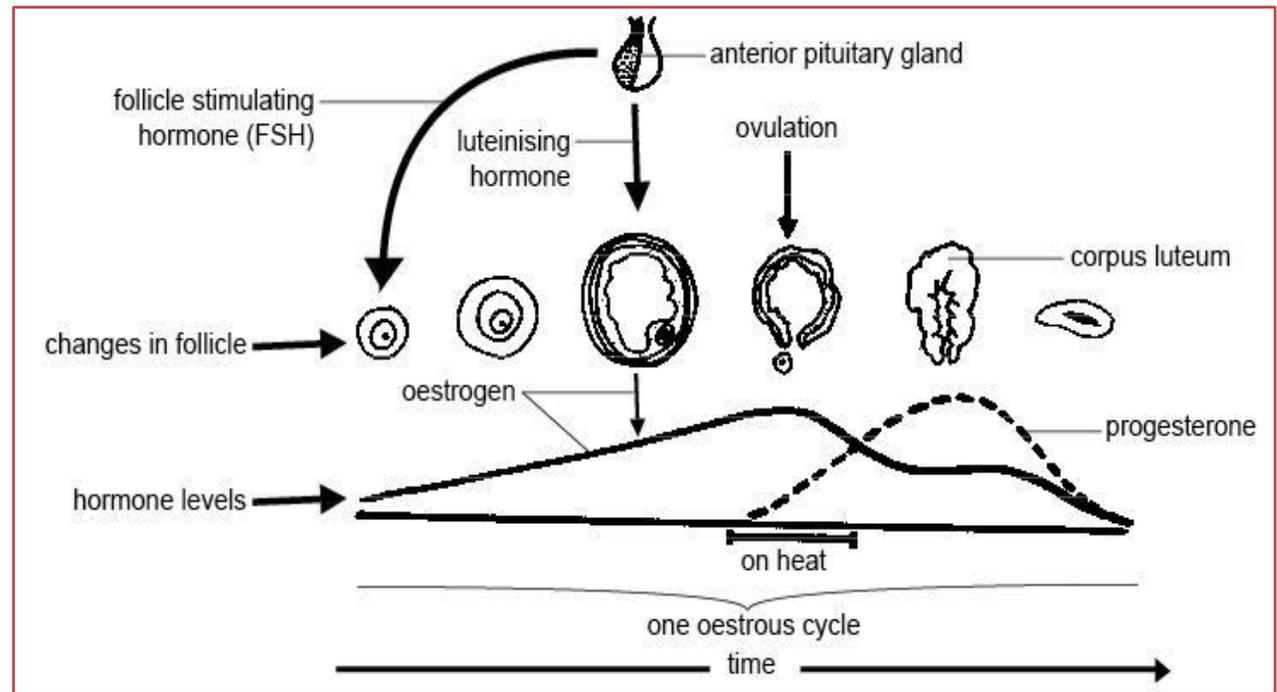
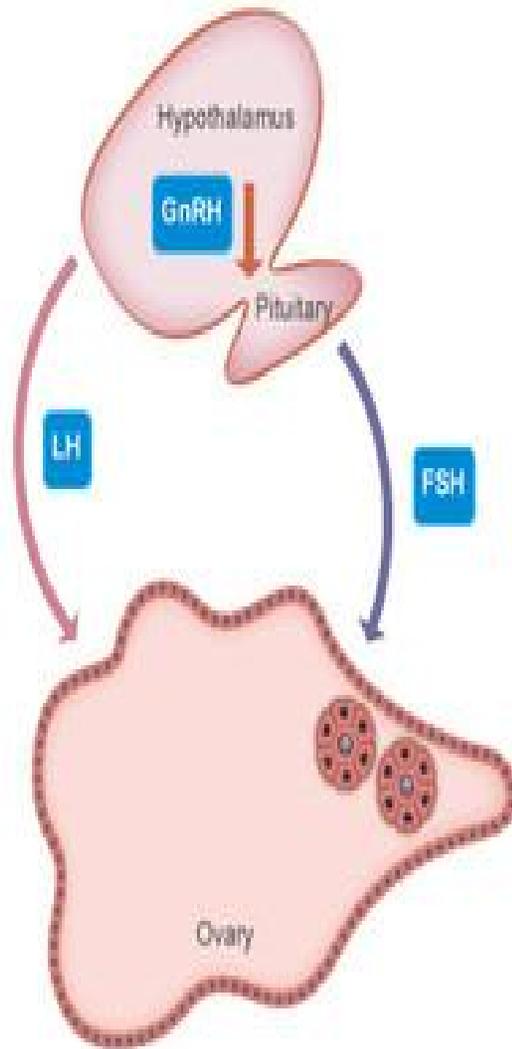
The increase in oestrogen observed during pro-oestrus, initiates several characteristic morphological changes in the uterus and vagina. This rise in oestrogen also suppresses release of **luteinising hormone-releasing hormone** (LHRH) by the hypothalamus, as well as directly inhibiting pituitary secretion of both LH and FSH. Negative feedback control of pituitary FSH secretion is also achieved by the peptide inhibin, produced by the granulosa cells of the maturing follicle. The various hormonal interactions of the HPO axis are summarised below:

Gonadotrophin secretion by the anterior pituitary is regulated by LHRH, produced by the hypothalamus. LHRH is transported along the axons of hypothalamic neurones to the *median eminence* where it is secreted into the *hypothalamic-hypophyseal portal system* and transported to the anterior pituitary. The hypothalamus secretes LHRH in rhythmic pulses; this pulsatility is essential for the normal activation of gonadotrophs and subsequent release of LH and FSH. Ovulation is triggered by an oestrogen-mediated preovulatory LH surge. Oestrogen levels rise during the morning, peak around midday and then fall during the afternoon of prooestrus. Once peak oestrogen levels are reached its inhibition of LHRH and gonadotrophin secretion ceases. At this point, oestrogen starts promoting both hypothalamic LHRH release and anterior pituitary responsiveness to LHRH. This positive oestrogenic modulation of hypothalamic-pituitary function results in a preovulatory LHRH surge and corresponding surge in LH.

The LH surge, which closely follows the oestrogen peak, occurs during the afternoon of prooestrus and triggers ovulation approximately 10 -12 hours later. FSH levels peak twice in the rat; the first (preovulatory) peak is LHRH-dependent and occurs in concert with the LH peak. This is followed by a second (postovulatory) rise in FSH that occurs at the time of ovulation or shortly after. This secondary FSH elevation is thought to be LHRH-independent, reflecting reduced inhibin synthesis by the postovulatory follicle. The rat corpus luteum is functionally short-lived and regresses in the absence of prolactin stimulation. Progesterone levels start to increase during prooestrus and peak during ovulation. Like oestrogen, progesterone feedback control of hypothalamic-pituitary function may be negative or positive, depending on the stage in the oestrous cycle. Following ovulation, progesterone synergises with oestrogen to inhibit gonadotrophin secretion. Conversely, rising progesterone levels during prooestrus trigger hypothalamic LHRH secretion, stimulating gonadotrophs in the anterior pituitary and reinforcing the preovulatory LH surge.

After ovulation, luteinisation of the follicular granulosa and thecal cells occurs resulting in the formation of the corpus luteum. The rat corpus luteum secretes progesterone autonomously for approximately 48 hours before becoming non-functional and degenerating over the course of several subsequent oestrous cycles.

Function of GnRH via LH & FSH



Prolongation of corpus luteum function requires continued pituitary secretion of prolactin, a luteotrophic and luteolytic hormone in the rat. Prolactin levels peak and fall simultaneously with the preovulatory prooestrus LH surge in normally cycling rats; this is followed by a secondary surge of prolactin around the afternoon of oestrus. The prooestrus surge of this hormone is thought to promote the lysis of corpora lutea from previous oestrous cycles.

Copulation during oestrus causes vagino-cervical stimulation which triggers, via a neuroendocrine reflex, twice daily prolactin release by lactotrophs in the adenohypophysis. This mating-induced prolactin secretion is luteotrophic in effect and disrupts normal oestrous cyclicity by maintaining the newly formed corpus luteum in a functional state, thus prolonging dioestrus.

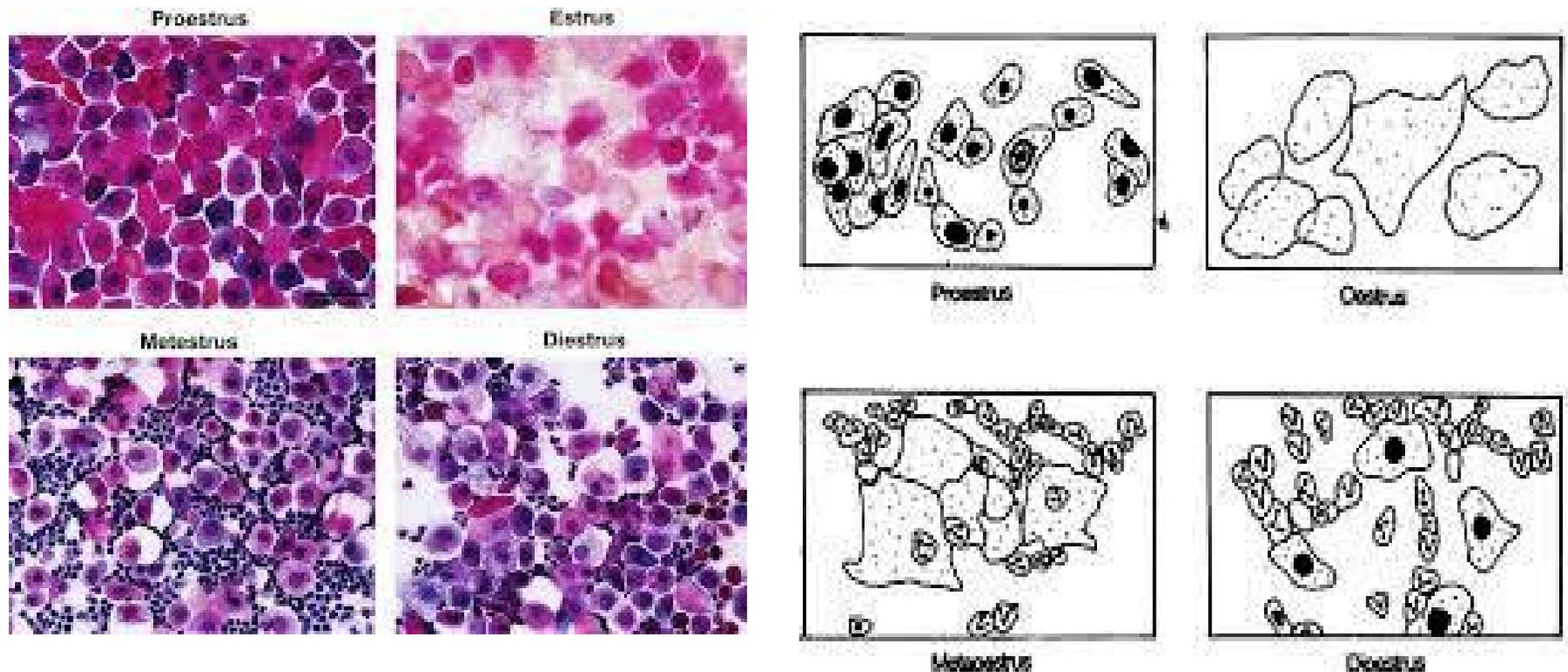
The continued secretion of progesterone during this lengthened dioestrus phase initiates development of the endometrium in preparation for implantation of the fertilised ovum, as well as initiating and maintaining vaginal mucification. If the mating is sterile or implantation fails to occur the corpus luteum regresses, terminating the prolonged dioestrus phase (referred to as **pseudopregnancy**) after 12-14 days and allowing resumption of normal reproductive cyclicity.

Conclusion

The rat has been elected as the main animal model in several studies involving reproduction. In female rats, **Gonadotropins: luteinizing hormone (LH)** and **follicle-stimulating hormone (FSH)**, are produced exclusively in **gonadotropin cells** of the anterior pituitary and secreted into the blood where they regulate **steroidogenesis** and **gametogenesis** in the gonads. The synthesis and secretion of LH and FSH are influenced by GnRH. The synthesis and secretion of LH and FSH are arranged either **positively** or **negatively** by *gonadal peptides* and *gonadal steroids*.

levels caused by ovarian activity under the influence of pituitary hormones. Changes in reproductive hormone levels further lead to structural changes in the uterus and vagina. The estrous cycle is a recurrent process that describes changes in reproductive hormone levels (Fig) as well as in reproduction tract network. The length of the estrous cycle and the frequency of the reproductive cycle in each organism are different. In mice, the estrus cycle lasts for about 4-5 days, and during this period, vaginal mucosa displays remarkable structural changes (Fig).

Histological changes in Vaginal Wall (SMEAR)



White rat (*Rattus norvegicus albinus*). Histological changes in the vaginal epithelium during oestrus cycle

Fig. 2. Histological features of vaginal mucosa during estrus cycle in rat.

RAT ESTRUS: SUMMARY

The reproductive cycle of female rats is called estrous cycle and is characterized as **proestrus**, **estrus**, **metestrus** (or diestrus I) and **diestrus** (or diestrus II). The ovulation occurs from the beginning of proestrus to the end of estrus. From the onset of sexual maturity up to the age of 12 months, the mean cycle length in the female rat is 4 days, and this short cycle length makes the rat an ideal animal for investigation of changes occurring during the reproductive cycle. Although rats ovulate spontaneously, they do not develop a fully functional corpus luteum unless receive coital stimulation. Fertile mating leads to pregnancy, but infertile mating leads to a state of pseudo-pregnancy lasting about 10 days.

During the estrous cycle, **prolactin**, **LH** and **FSH** remain low and increase in the afternoon of the proestrus phase. **Estradiol** levels begin to increase at metestrus, reaching peak levels during proestrus and returning to baseline at estrus. **Progesterone** secretion also increases during metestrus and diestrus with a decrease afterwards. Then the progesterone value rises to reach its second peak towards the end of proestrus.

Q & A

What is oestrous cycle in animals?

The Br. term, **oestrous cycle** (U.S: **estrous cycle**) is the reproductive system in most mammals other than primates. Reproductive hormones cause the **cycles** to start after puberty in sexually mature females. They are interrupted by non-breeding phases or by pregnancies. Usually **estrous cycles** continue until death.

Which are the hormones in charge of this regulation?

GnRH ultimately controls reproduction. *GnRH* is synthesised and released by the neurons of the *hypothalamus* in the form of pulses or surges. Each secretion of *GnRH* provokes production and secretion of *FSH* and *LH* by the anterior *pituitary* gland.

What are the four phases of the estrous cycle?

The estrous cycle can be divided into four stages: **proestrus**, estrus, metestrus, and diestrus. During **proestrus** the CL regresses (progesterone declines) and a preovulatory follicle undergoes its final **growth** phase (estradiol increases). **Ovulation** usually occurs during estrus (cows ovulate during metestrus).

What hormone controls the release of the egg at ovulation?

luteinizing hormone (LH).....The process of ovulation is controlled by the hypothalamus of the brain and through the release of hormones **secreted** in the anterior lobe of the **pituitary** gland, **luteinizing hormone (LH)** and **follicle-stimulating hormone (FSH)**.

What stage of the estrous cycle where does ovulation occur?

The estrous cycle can be divided into four stages: **proestrus**, estrus, **metestrus**, and diestrus. During **proestrus** the CL regresses (**progesterone declines**) and a pre-ovulatory follicle undergoes its final growth phase (**estradiol increases**). Ovulation usually occurs during estrus by sudden fall of LH (cows ovulate during **metestrus**).

What happens in the oestrous cycle?

The **oestrous cycle** (U.S: estrous **cycle**) is the reproductive system in most mammals. Reproductive hormones cause the **cycles** to start after puberty in sexually mature females. They are interrupted by non-breeding phases or by pregnancies. Usually estrous **cycles** continue until death.

What is heat period in a woman?

Unlike other mammals, which go into "**heat**" during fertile **periods**, **women** can be up for sex any time of the month. Evolutionary theorists have tried at several explanations for the loss of this estrus cycle in humans, one of the most common being that humans lost the "**heat**" phase to conceal ovulation.

What is the difference between menstrual cycle and estrous cycle?

Menstrual cycle occurs in primates whereas **oestrous cycle** usually occurs in non-primate animals. During **menstrual cycle**, sexual receptivity may occur throughout the **menstrual cycle** whereas in **oestrous cycle** sexual receptivity occurs usually in **between** the **oestrous cycle**.

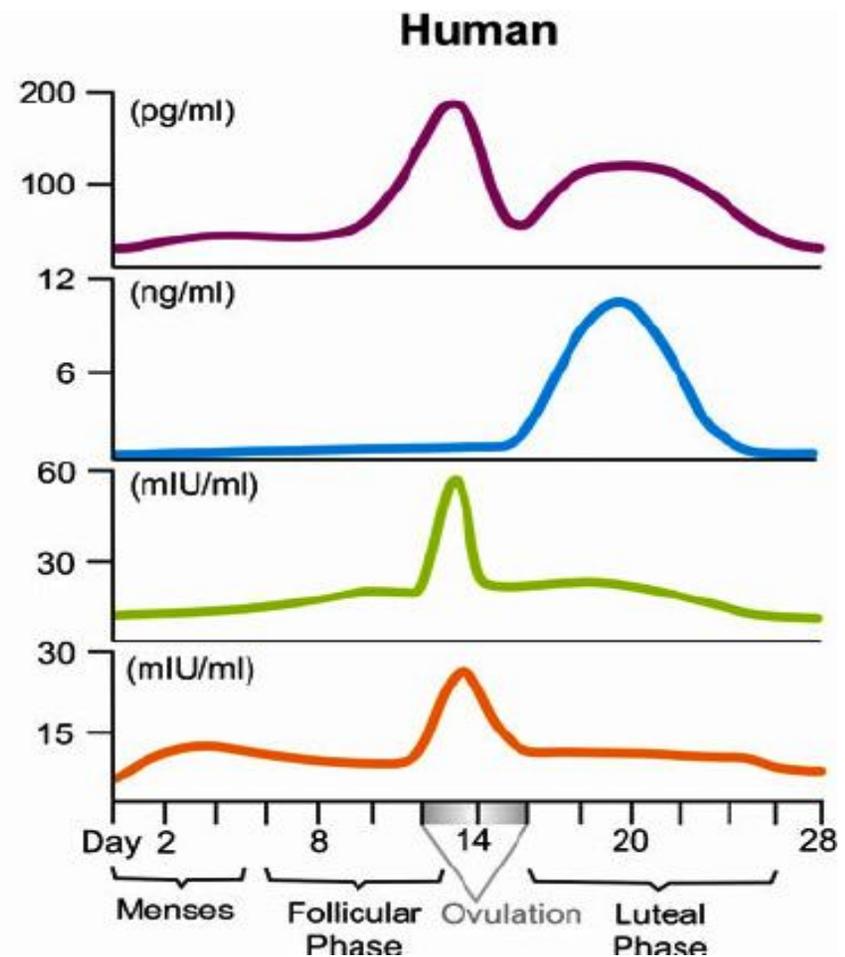
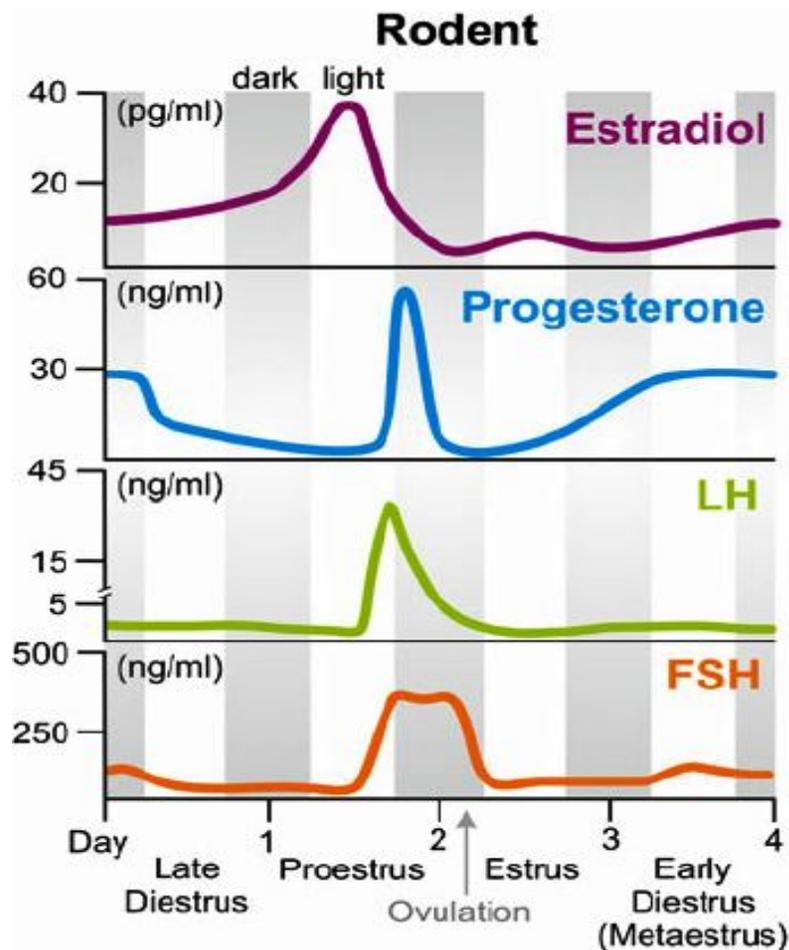
Can humans be in heat?

No...This is also referred to as being "in **heat**". In contrast, females of species with menstrual cycles **can be *sexually active at any time in their cycle***, even when they are not about to ovulate. **Humans** have menstrual cycles rather than estrous cycles, but do not usually show "heat", rather a highly modified form of sexual receptivity, the mild, suppressible urge of receptivity.

Do female apes have periods?

Beyond **primates**, it is known only in bats and the elephant shrew. **Females** of other species of placental mammal undergo estrous cycles, in which the endometrium is completely reabsorbed by the animal (covert menstruation) at the end of its reproductive **cycle**.

Variations in the Levels & Peaks of 4 Hormones during Estrus & Menstrual Cycles



Q to A

What is Anestrus? Give Example

What is Monoestrus? Give Example

What is Biestrus? Give Example

What is Polyestrus? Give Example

What is Prepartum Estrus? Give Example

What is Postpartum Estrus? Give Example

What is called Lactation Unestrus? Give Example

What do you mean by Delayed Fertilization? Cite Example

What do you mean by Embryonic Diapause? Cite Example