9. REPRODUCTIVE ENDOCRINOLOGY

ENDOCRINE TISSUES
There is a variety of hormones involved in the regulation of reproduction in females. These hormones are produced by different tissues throughout the organism (Figs. 9-1, 9-2).

Endocrine tissues directly involved in reproduction

- Hypothalamus
- Hypophysis
- Ovary
- Placenta
- Fetus
- Uterus
- Testes

Figure 9-1. Tissues that are recognized as producing hormones involved in reproduction

Reproductive hormones

Releasing factors, GnRH
Inhibiting factors, PIF
Oxytocin
Gonadotropins: FSH, LH
Prolactin, placenta lactogens, relaxin
Steroids: Es, P₄, androgens, glucocorticoids
Exogenous gonadotropins: hCG, MSG
Prostaglandins: PGF₂α, PGE₂

Figure 9-2. Some of the most common or better understood reproductive hormones

Hypothalamus
Gonadotropin Releasing Hormone (GnRH): Responsible for stimulating the release of gonadotropins from the pituitary.
Prolactin inhibitor factor (PIF): Inhibits prolactin release.
Oxytocin (Ot): Stimulates smooth muscle contraction in the uterus and the mammary gland; it also stimulates PGF₂α in the uterus.

Hypophysis
Follicular Stimulating Hormone (FSH): Stimulates follicular growth and estrogen secretion.
Luteinizing Hormone (LH): Triggers ovulation and corpus luteum formation; stimulates progesterone, testosterone, and estrogen secretion.
Prolactin (Prl): Sustains lactation and maintains CL function.

Ovary
Estrogens (Es): Responsible for the modulation of sexual behaviour, secondary sex characteristics, growth of the reproductive tract, uterine contraction, mammary duct growth, gonadotropin secretion, calcium uptake and a general anabolic effect.
Progestins: In conjunction with estrogens, influences estrus behaviour, prepares the uterus for implantation and stimulates endometrial secretion, maintenance of pregnancy, alveolar growth and gonadotropin secretion.
Androgens: Precursors of estrogens in the follicle.
Relaxin: Relaxation of the pelvic symphysis during parturition.
Activin: Stimulates FSH secretion.
Inhibin: Inhibits FSH secretion.

Placenta
Human chorionic gonadotropin (hCG) is a hormone produced in humans that has LH activity and plays a role in the maintenance of CL. It is Present 8-10 days after fertilization, and it appears to be the signal of pregnancy only in humans.
Pregnant mare serum gonadotropin (PMSG) is a hormone with FSH like activity that promotes follicular development which results in accessory CL. It originates in trophoblast cells of the equine conceptus by the fifth week of gestation. Its high sialic acid content contributes to its long half-life.
Placental lactogens (PL): Has GH like capabilities, influences fetal development and lactation capacity (most species).
**Feto-placental unit**
Produces a variety of steroid hormones the most important are progesterone and estrogens in most species.

**Uterus**
- Prostaglandin F<sub>2α</sub>: A luteolytic hormone.
- Prostaglandin E<sub>2</sub>: Antilutolytic activity.

**ESTROUS CYCLE**

**Reaching Puberty**
Gonadotropin production. As an animal reaches puberty, there is an elevation in the production of adrenal androgens followed by an elevation in the concentration of gonadotropins. Gonadotropins are released in a pulsatile manner (Figs. 9-3, 9-4). The elevation in the gonadotropin concentration is the result of an increase in the frequency and amplitude of the pulses of GnRH (Fig. 9-3).

These events lead to follicular development in the ovary with the consequent elevation in circulatory estrogens. Folliculogenesis culminates with one successful ovulation, at which time the animal is considered to have attained puberty (Fig. 9-4).

**Non-cycling animals**
Non-cycling animals secrete GnRH in pulses but at low amplitude and a low frequency. Increasing the frequency of these pulses will result in increased pulses of LH, which in turn will culminate with ovulatory events; therefore, commencing cycling activity (Figs. 9-5, 9-6).

**Sex differences in GnRH secretion pattern**
The main differences between the secretion patterns of GnRH by the female and male animal is that the female secretes a high frequency of pulses of GnRH in the tonic centre and a large surge of GnRH by the ovulatory centre. Males continuously secrete small amplitude low frequency pulses of GnRH. The ability of the higher centers to release these sex linked GnRH secretion patterns is determined at the time of sexual differentiation and reinforced throughout the adult life.

By default, the animal's brain functions as a female's brain. It manifests a cycling pattern with surges, unless it is forced to perform in a male-like fashion that is to maintain continuous secretion.
The transformation from a female to a male pattern of secretion is under testosterone control, at the time of gonad formation during sexual differentiation. At this time, testosterone penetrates the blood-brain barrier; it is aromatized to estrogen and, as such, primes the ovulatory centre to not produce surges of GnRH, in response to high estrogen concentrations. To maintain the male pattern of secretion, the brain has to be reinforced during the early adult life of the animal by exposing the brain to elevated levels of testosterone.

Although estrogen is the hormone that primes the brain to behave like a male, the same phenomenon does not take place in the female. The estrogens circulating in the female organism at the time of sexual differentiation are bound to a much larger carrier, a glycoprotein called Alpha fetoprotein (α-FP) which cannot cross the blood brain barrier as testosterone does.

Age. The age at which an animal starts cycling varies with the species, the environment in which the animal is living—of special importance are temperature and photoperiod, and its nutritional status. The attainment of puberty is more closely related to the weight of the animal than to its age. Typical ages of puberty for sheep are six to seven months, if these are born in the spring and about 12 months if they are born in the fall. Swine and goats also reach puberty at about 7 months, while horses take between 15 and 18 months, and cattle takes about 12 months. Dogs range from 7 to 10 months or about 3 months after the bitch reaches adult weight. Cat’s average is 7 months or when the animal is about 2.3 - 2.5 kg.

General endocrine patterns during the estrous cycle

Once the animal reaches puberty and starts cycling there is a repeated pattern of hormone production. Figure 9-7 presents the individual concentration pattern for the most common reproductive hormones.

Phases. The estrous cycle is characterized by two phases or several stages, which represent the predominant endocrinological or behavioural event (Figs. 9-8, 9-9, 9-10). These are:

![LH PATTERN WHILE CYCLING](image1)

**Figure 9-6. Detailed secretion pattern of GnRH on a cycling animal**

HORMONAL PROFILES DURING THE CYCLE

![Figure 9-7. General endocrine profiles observed during the estrous cycle in most domestic animals](image2)

**PHYSIOLOGICAL PHASES OF THE ESTROUS CYCLE**

![Figure 9-8. The estrous cycle is divided in the follicular and luteal phase](image3)
Follicular phase. This phase represents the period of fast follicular growth. It is characterized by increasing production of estrogens.

Luteal phase. The luteal phase represents the period following ovulation in which the CL develops and predominates. Progesterone is the most abundant hormone during this phase.

Stages. The cycle can also be described in term of stages which more accurately describe the events taking place (Fig. 9-9). These are:

Proestrus. Proestrus corresponds to the beginning of the follicular phase during which the follicles are growing very fast and producing increasing amounts of estrogens (Fig. 9-9).

Estrus. In this stage the female becomes receptive to the male and the concentrations of circulating estrogens are the highest, ovulation takes place during or shortly after estrus. After ovulation, the follicular phase changes to the luteal phase.

Metestrus. This stage comprises the initiation of the luteal phase. Following ovulation, the follicle becomes the corpus haemorrhagic and the secretion and concentrations of estrogen decline significantly as the follicular cells start to mix, multiply, and become luteinized; they start to produce progesterone.

Diestrus. During this stage the corpus luteum is fully functional and the output of progesterone is large and sustained. It is the longest stage of the cycle. If the animal is bred and becomes pregnant then, this stage continues as pregnancy anestrus, which is a prolonged period during which the ovary does not resume cyclicity. During this period, the corpus luteum is maintained as the corpus luteum verum or corpus luteum of pregnancy. The CL secretes large amounts of progesterone for almost the entire duration of pregnancy.

If pregnancy does not take place, the CL regresses, eventually becoming the corpus albus, and the circulating concentrations of progesterone decline. The decline in progesterone concentration marks the end of the luteal phase and permits the resumption of the high frequency pulsatile secretion of GnRH. This in turn will trigger a significant release of gonadotropins and the resumption of follicular development, thus, commencing a new follicular phase (Fig. 9-8).

Length. The length of the estrous cycle varies depending on the species and with the individual. The following are observed ranges of cycles; cows, sows and goats: 20 to 21 days; ewes: 16 to 24 days, 16 being more typical; mares: 20 to 24 days.

Ovulation takes place about 24 to 30 hours after the beginning of estrus in the ewe, between 30 and 36 hours in the goat, and between 35 to 45 hours in the sow. In the cow, ovulation occurs 9 to 11 hours after the end of estrus, while in the mare ovulation takes place 1 to 2 days before the end of estrus.
As in most domestic animals, the cyclic activity in humans is also described based on the most visible element of the cycle. In animals, what is clearly recognizable is the behavioral evidence that a female is in standing heat or estrus, thus, the name of estrous cycle. In humans, the reference point is menstruation, thus, the menstrual cycle (Fig. 9-10).

The menstrual cycle is considered to start with the initiation of menstruation. This correlates with the initiation of the follicular phase of the cycle (Fig. 9-10). Following the menses, which last 4-5 days, the follicle continues to develop until there is enough estrogen in circulation to trigger the release of the LH surge. The LH induces ovulation and, at this point, the luteal phase commences. The ovulated follicle evolves into a CH and then to a functional CL, thus the predominant hormone during this phase is progesterone. Unlike domestic animals, humans and primates do not manifest heat and can copulate at any time during the cycle. A comparison of the relative hormone concentrations in both the estrus and menstrual cycle is presented in figure 9-11.

Breeding time. Breeding or insemination should be aimed at maximizing the chances of having viable sperms at the fertilization site, at the time the ova is released. Breeding should take place about 14 hours before ovulation or almost at the end of estrus in the cow. In the ewe, better results are obtained if breeding takes place in the middle or in the second half of estrus. In the goat, breeding 10 hours after the onset of estrus is ideal. In sows, late on the first day and/or early on the second day of estrus is the best approach. Finally, in mares, breeding at the time of ovulation yields best results.

Types of animals
Under natural conditions, most species breed during a time which will allow them to give birth when food is more plentiful, in order to improve the chances of survival. Given that different species have different gestation lengths, the breeding time takes place at different times of the year. In some domestic species, this trait has been selected out, almost completely in order to maintain continuity in animal production in species such as dairy cattle and swine. This has generated several types of animals (Fig. 9-12).

<table>
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<tr>
<th>TYPE OF ANIMALS</th>
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<tr>
<td>Polyestrous (continuous breeders)</td>
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<td>Seasonal polyestrous (short day breeders)</td>
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<td>Seasonal polyestrous (long day breeders)</td>
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<td>Monoestrous</td>
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Figure 9-12. Types of animals based on the frequency and/or season of cycling activity

Polyestrous. The term implies that, if the animal does not get pregnant, many cycles will take place consecutively. Being a continuous breeder further indicates that the animal can cycle during the entire year, independently of environmental cues. Cows, sows, rats, and primates belong to this group (Fig. 9-13).

Seasonal polyestrous animals: Are those which only cycle during a determined season. They start cycling in response to specific environmental cues, such as an increase or decrease of light hours. Within this classification, we can identify short and long day breeders.

Short day breeders such as the ewe, nanny and doe, start cycling as the days get shorter in the fall (Fig. 9-14).

Long day breeders, on the other hand, are animals such as the mare that start cycling as the days are getting longer in the spring (Fig. 9-15).
Cats also tend to cycle when days are getting longer in the early spring. Cats however, are induced ovulators, which means that the release of the LH surge that triggers ovulation only takes place as a result of copulation.

During the period when seasonal breeders are not cycling they enter into seasonal anestrus, if they are not pregnant.

**Monoestrus.** These are animals which have only one cycle per year. In this category we find the wolf, and the fox. A bitch cycles about 3 times in two years. All these animals have a much longer period of estrus than other domestic animals (Fig. 9-16).