REGULATION OF ESTROUS CYCLICITY AND ENDOCRINE BASIS

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Importance:

The main purpose of the animal industry is to develop an animal for growth and reproduction at a faster and economical rate. Since, the growth processes are under endocrine control and the reproductive processes are primarily under endocrine control. Thus, it is important areas of physiology which are concerned with growth and reproduction to develop sound agriculture which deals with health and economics of human being. Thus, it helps to maintain and improve the efficiency of animal production.

Endocrinology being able to co-relate anatomy, physiology, genetics and biochemistry and thus helps in diagnosis of clinical cases.

For economic dairying, it is essential that pregnancy diagnosis is achieved at the earliest & this can be done with the help of different assay of hormones from milk/blood. Thus, we can reduce calving intervals which is an trait for efficient dairying.

Organisation: All animals consists of two interlocking systems 1) Endocrine system & 2) Nervous system. These two systems usually functions as a unit. The hormones (Secretions of endocrine glands) interplays that produce the final results.

Changes in the female genital organs during the various phases of the sexual cycle and their regulation (Estrous Cycle):

Rhythmic sexual behavior patterns develop in female animals during puberty this behavioral change (sexual receptivity) is called as estrus. It means mad desire also referred it by a term “heat”. It occurs with each estrous cycle in nonseasonal breeders unless pregnancy intervenes.

The combination of physiological events which begin at one estrus period and end at the next is termed as estrous cycle or with the approach of puberty all females exhibit a well marked functional rhythm of reproductive system which in the domestic animals is called the estrous cycle. Though each species has its own peculiarities in respect to the pattern of estrous cycle, basically all are similar.
The rhythm of the reproductive cycle is largely dependent upon the functional activity of the hypophysis and the ovary which leads to several physiological changes in the reproductive tract.

**Hormonal Control of Estrous Cycle** :- Hormonal Control of estrous cycle is dependant on the interrelated action of gonadotrophic hormones secreted by the ant. pit. and the gonadal hormones secreted by the ovary. Follicular growth and maturation of ovum is caused by the FSH. As follicle grow oestrogen secreted by them enters in circulation in increasing amounts. LH in conjunction with FSH stimulates these internal cells of follicle to secrete oestrogen. The LH causes preovulatory enlargement of follicle.

**Phases of estrous Cycle** :- The estrous cycle is commonly divided into 4 phases i.e. Proestrus, Estrus, Meterstrus and Diestrus. However, based on the hormonal status of the animal. This cycle/period can be conveniently classified into

1. **Estrogenic/Follicular/Proliferative Phase** :- This comprising of Proestrus and estrus periods. The ovaries are under the influence of the FSH for development of Graffian follicle and hence this period is called follicular phase of the cycle.

2. **Progestational/Luteal/secretory Phase** :- This comprising of metestrus and diestrus periods, the ovaries are under the influence of LH. This period is known as the luteal phase of estrous cycle. The follicular phase of the cycle is characterized by rapidly decreasing levels of progesterone and a peak levels in blood levels of estrogen. This decline in the level of progesterone followed by the rapid rise in estrogen is essential requirement for the onset of behavioral estrus.

**1. Proc trus** :- It is the period after the CL fails. when the progesterone level drops, FSH release stimulates follicle growth, and rising estrogen levels lead to estrus.

**In Cow** :- The proestrus period is characterised by follicular growth and estrogen production. Estrogen increases blood supply to the tubular genitalia tract and causes edema from the vulva to uterine tubes, especially in Uterus. The vulva swells to some extent, Vestibule becomes hyperemic, the glands of cervix and Vagina secrete a serous secretion which appears a thin vaginal discharge. The growth of ovarian follicle as Graffian follicle. The drop in progesterone on days 16 and 17 allows FSH release, follicle to grow and estrogen output.
It is accompanied with the following changes:

1. Growth of G. F. under influence of FSH.
2. Theca internal secretes increasing amounts of estrogens.
3. Increased amount of estrogen in circulation.
4. Elimination of increasing amount of estrogens in Urine.
5. The C.L. undergoes rapid degeneration both in morphology and function.
6. Decreasing amount of progesterone in circulation.

The increasing amount of estrogen in circulation causes changes in the female genital organs:

a) Edema and swelling of Vulva
b) Increased Vascularity of secondary Organs of reproduction (Vagina and Uterus)
c) Gradual cornification of vaginal epithelium in rats, dogs and cats.
d) Microscopic examination of vaginal smear from rats exhibit many large nucleated mucosal cells but no leucocytes.
e) Gradual relaxation of cervix.
f) Increased secretion of mucus from goblet cells of cervix & vagina.
g) Increased vascularity of endometrium and bleeding in bitches.
h) Growth of cell and cilia lining the oviduct.
i) The animal tends to show interest in male at late stages.

2. Estrus:– At the end of 3 or 4 days of proestrus, estrus, the period of self desire appears. This is a result of estrogen acting on the CNS of body and bringing about psychic manifestations of heat. During 14-18 hrs. Cow is in estrus, she becomes restless, anxious bellows and loses her appetite, decrease in milk production. The genital tract is under increasing dominance of estrogen. Congestion of genitelia occurs. There is mucus discharge from vulva. Apparently this discharge has an odor (sex pheromone) that attracts and arouses the bull. The uterus is stimulated showing strong myometrial tone and erect uterus condition. The vulva and vagina continue to swell and show hyperemia. Finally at the end of 14-18 hrs. She shows psychic manifestation of heat, by attempting mount on other cow.
While level of estrogen has been rising the level of FSH has begun to decline. A rising level of LH from pituitary beings during proestrus and causes estrogen release. This LH surge which peaks at metaestrus will cause ovulation and aid in formation of CL.

**Duration of Estrus**: The estrus period is avv. 17.8 hrs. In dairy cows and 15.3 hrs. in dairy heifers. The cow is different from most of farm animals, since she has such a short period of sexual receptivity and ovulation does not occur until 12-16 hrs. after the end of estrus.

**Estrus Characters**:

1) The desire of female to accept the male. Bovines generally show signs of homosexuality which can be marked from a distance.

2) The female seeks out the male and accepts him.

3) The changes of proestrus are intensified in estrus as follows:

   1. The GF becomes large and mature.
   2. The ovum undergoes maturation changes.
   3. The oviduct becomes tonic and exhibits spontaneous movement.
   4. The epithelium of the oviduct matures and cilia become active.
   5. The fimbriae of the oviduct arrange themselves close to the graffian follicle.
   6. The blood supply to entire reproductive tract is increased. The m.m. of vagina exhibits congestion.
   7. The m.m. of the oviduct grows rapidly and secretes increasing amount of fluid.
   8. There is increased migration of leucocytes in uterine lumen.
   9. The goblet cells become well developed and secrete mucin, hence secretion of mucus is increased.
  10. The vulva becomes relaxed and edematous and string of mucus may hang out.
  11. The cervix becomes relax and pliable.
  12. In cow ovulation occurs about 12 hrs. after the end of estrus. In cat, ovulation doesn’t occur until coitus takes place. Hence, the stage of estrus in non-spontaneous evaluators may be prolonged in absence of coitus.
  13. In many species, like dog, cat, rat etc. the cornified vaginal epithelium undergoes desquamation. Thus vaginal smear shows high % of cornified epithelial cells.
3. Met-estrus:— The period immediately following cessation of heat is metestrus. This is the period during which ovulation occurs. Hemorrhage fills the follicular cavity and luteal cells begin rapid growth. This is the period of CL development. Following ovulation, progesterone begins to rise. FSH, LH and estrogen have return to basal level. The congestion of genital tract diminishes and glandular secretions from tract decreases.

Metestrus lasts about 2-3 days. During this, bloodstained mucus is discharged from the vulva. (Pseudo-menstruation).

During metestrus, ovulated egg is picked up by uterine tube and transported toward tubal-uterine Junction. Fertilization occurs in the upper portion of the uterine tube. If not fertilized, egg begins degeneration.

Changes in reproductive Organs during metestrus:—

1. In cows, during early part of metestrus the epi. over the caruncles becomes highly hyperemic and some capillary hemorrhage may occur which is known as menstrual-bleeding. This is because of estrogen withdrawal.

2. There is gradual loss of tone of the oviduct and the uterus becomes soft and pliable to touch.

3. This period is followed by diestrus and in seasonally monestrous animals it is followed by either a period of anestrus or pseudo pregnancy if pregnancy does not occur.

Microscopic examination of vaginal smear from rats exhibits large number of leucocytes.

4. Diestrus:— It is the longest period of estrus cycle, and is characterized by presence of CL and high level of circulating progesterone. Even though the cow does not become pregnant, the CL secretes progesterone affect the primary development and uterine growth. The myometrium hypertrophies and uterine gland secretes a thick viscid material which will nourish the zygote. If the ovum is not fertilized the CL remain functional until about 17 days when luteolysin causes it to regress in preparation for a new cycle.

Changes of reproductive tract during diestrus:—

1. Differentiation of the endometrium. Endometrium thickens and the uterine glands undergo hypertrophy.

2. The cervix becomes constricted and cervical and vaginal mucus scant

3. The m.m. of vagina becomes pale.
4. At late diestrus, the CL begin to show regressive changes accompanied with retrogressive changes in the endometrium and uterine glands.

5. If pregnancy set up in the CL of estrous cycle continues to function which is then known as CL of pregnancy.

6. In case of non-pregnancy, this period is followed by appearance of proestrus in polyestrous animals.

7. Microscopic examination of vaginal smear from rats exhibits decreasing number of leucocytes and presence of non-nucleated mucosal cells.

**Anestrus** :- It is the period during which the ovaries and reproductive tracts are in quiescent state (resting state). It is characterised by absence of CL in the ovaries, pale Vaginal mucosa, tightly closed cervix, and loss of uterine tone. Many a times after calving, cow may exhibits lactational anestrus which is primarily due to draining off of nutritive materials & suckling effects.

It is presumed that high level of circulating prolactin makes the ovaries refractory to the influence of FSH from anterior pituitary.

**Levels of reproductive hormones in blood during estrus cycle** :-

1. **Gonadotrophins** :- The pattern of gonadotrophin levels in blood during estrous cycle is essentially the same in almost all domestic animals

   a) The level of LH in ewes and cows ranges between 0.2 to 2.0 ng/ml in plasma during entire luteal phase. But at estrus there is surge of LH and the level may reach 50-100 ng/ml plasma.

   b) The level of FSH remains high 30-80 ng/ml, plasma in cows during entire course of estrous cycle. However it reaches a peak approx. 100 ng/ml plasma in cows.

2. **Gonadal Hormones** :-

   1) The level of estrogen (estradiol 17β) in cattle fluctuates around 100 pg/ml, plasma almost for entire luteal phase and reaches about 175 pg/ml on the day prior to estrus.

   2) The level of progesterone in circulation in cattle remains low as less than 1ng/ml plasma but shows an increasing trend from about day 2 of the estrus and reaches a peak level of 6-7 ng/ml plasma around day 12, and remains at that level upto around day 17, after which there is a steep decline in the level in case of non-pregnancy.
In summary, it can be seen that, estrogen dominates about 4 days of the cycle where as progesterone dominates about 17 days. Thus period of follicle-estrogenic phase and period of luteum (CL) progestational phase. The duration of estrus and length of estrous cycle vary from species to species which is as follows.

**Gonadotropin hormones of anterior pituitary:** Two hormones from the adenohypophysis affect the gonads: follicle stimulating hormone (FSH) and luteinizing hormone (LH) (interstitial cell-stimulating hormone). FSH and LH exert their effects entirely on reproduction. FSH and LH regulate the production of sex gametes and the secretion of hormones from the gonad. LH required for spermatogenesis because of its role in testosterone production. FSH is important for the completion of meiosis of germ cells through its influence on sertoli cell activity. The nomenclature of gonadotropins given according to their principal biologic effects.

1) The hormone that caused ovulation and transformation of the ovarian follicle to a corpus luteum was called luteinizing hormone (LH). Because this hormone also stimulates the leading cells or interstitial cells of the testis. It was also called as interstitial cell-stimulating hormone (ICSH).

2) The other pituitary gonadotropin called follicle stimulating hormone (FSH) because this fraction promoted the development of graffian follicles in the ovary.

**Follicle-Stimulating Hormone (FSH):** It is a glyco-protein hormone (the hormones are composed of chains of Amino acids linked together by peptide bonds and chains of carbohydrates linked to the polypeptides hence called glyco-proteins) with a molecular weight of 25,000 in human, 32,000 in sheeps, and consists of 2 non-identical, non-covalently linked sub units the alpha and beta chains. The beta chain varies in length from 110-120 a.a. and confer the specific biologic activity to FSH. While the alpha chain is some what shorter and is essential to maintain the activity of FSH. The carbohydrate portion of FSH contains sialic acid, hexose and hexosamine.

**Histological functions:**

A) Ovarian follicle by
   a. Stimulating mitotic proliferation of ovarian granulosa cells.
   b. Stimulating secretion of follicular fluid
B) Seminal tubules and influences spermatogenesis.

Site of action: Ovary, testis (seminiferous tubules) [functions - follicular growth, stimulation of Sertoli cells for spermatogenesis].

In female: FSH stimulates the growth and maturation of the ovarian follicle. FSH does not have cause secretion of oestrogen from the ovary by itself but in the presence of LH it stimulates oestrogen production from either ovary or testis.

In males: FSH acts on the germinal cells in the seminiferous tubules of the testis. It is also responsible for spermatogenesis up to the secondary spermatocytes. FSH is primarily used in the stimulation of follicular development to induce multiple ovulation for embryo-transfer techniques.

Before puberty, development and regression of the follicles is latter independent of the action of FSH since, the level of FSH remains very low. With the approach of puberty there is an increase in secretion of FSH and the development of ovarian follicle is influenced. There is an increase in the level of FSH before oestrus which reduces with the increase of oestrogen. However it promotes spermatogenesis.

2) Luteinizing Hormone (LH): LH is a glyco-protein with a molecular weight of 30,000 daltons and a half life 30 minutes. The pituitary content of LH is highest in cattle, sheep, and cats and lowest in horses and man.

Site of action: Ovary, testis – Leydig cells.

Functions: Ovulation, CL formation, secretion of progesterone, oestrogen and androgen

Physiologic functions:

1) In females:
   a) It stimulates FSH primed follicular cells to secrete oestrogen.
   b) It promotes maturation of the graffian follicle to the stage of preovulatory swelling in combination with FSH.
   c) Causes ovulation from a matured follicle, the process of ovulation seems to be under the influence of certain proteolytic enzymes. The proteolytic enzymes are supposed to act through the intermediates of histamine.
   d) It helps in formation of corpus luteum (CL)
e) In some species of animal helps in maintenance of CL and secretion of progesterone.

f) May also act upon non-germinal cells of the ovary to produce androgens.

2) In males:— It acts upon interstitial cells to differ them into leydig cells which in turn secretes the male hormone. Hence, it is known as interstitial cell stimulating Hormone (ICSH), which acts directly on leydig cells of testis, causing testosterone production which in turn acts throughout the body as well as on seminiferous tubules which plays an important role in the maintenance of spermatogenesis.

**Estrogen & progesterone and their actions.**

**ESTROGENS:**

Estrogens have been isolated from the ovaries, adrenals, placenta and even the testis of the male. In a cycling female, estrogen is produced by interstitial cells of the ovary and theca cells of the growing follicle under the influence of FSH and LH.

Estradiol is the primary estrogen with estrone and estriol representing other metabolically active estrogens. All estrogens secreted by the ovary are produced from androgenic precursors.

**Chemistry:** All gonadal hormones are lipid compounds known as steroids. All steroids have a common cyclopentanoperhydrophenanthrene nucleus composed of 3, six membered phenanthrene rings designated A, B and C and one five-membered cyclopentane ring D. The basic nucleus contains 17 carbon atoms, carbon 18 and 19 called angular methyl groups project from carbon 13 and 10 respectively.

Addition of an angular methyl group representing C 18 gives rise to estrane, the parent structure of estrogens.

**Hormone synthesis and release:** The ovary secretes 3 hormones two steroids and one protein in nature which are as follows:

1. **Estrogen**
2. **Progesterone.**
3. **Relaxin → Protein.**

The luteal cells, theca cells and leydig cells use cholesterol to produce specific steroids according to their enzymatic profile;
Estradiol is considered to be the principle follicular hormone. It circulates and get metabolized to estrone and subsequently to estriol. It is metabolized/inactivated in liver.

Estrone and estriol finally combine with glucoronic acid/sulphates and are eliminated in urine as a soluble steroid.

Out of these 3 naturally occurring estrogens, 17α estradiol is the most potent while estriol is the least, this can be roughly given as

$$1 \text{ Estradiol} = 10 \times \text{ Estrone} = 50 \times \text{ Estriol}.$$ 

Other synthetic estrogens are – Dienestrol, Hexestrol, Benzestrol, promethestrol etc. and are closely related to Diethylstilbestrol in structure.

The naturally occurring estrogens are secreted by :-

1) Ovary (Theca Internal Cells), 2) Placenta (syncytial Cells), 3) Testes (Sertoli Cells), 4) Adrenals (Zona fasciculate).

Here, Ovary is the primary site of its secretion in non-pregnant females whereas placenta is the chief source in pregnant animals. Production of estrogen from testis is under control of LH. The urine of stallion contains significantly high levels of estrogens.

The estrogens are secreted into the blood in free form as free estradiol but get quickly bound with plasma proteins (albumin / specific binding globulin).

Mode of Action :- Steroids are supposed to act through induction of enzyme synthesis at the nuclear level in the target tissues. The estrogens may also act as a cofactor in a transhydrogenation reaction. In which H⁺ ions and electrons are reversibly transferred between DPN and TPN.

Physiologic functions of Estrogens :- The effect of estrogens on different system is mentioned below.

1. Action upon Hypothalamo-Hypophyseal Axis :- The relationship between FSH and estrogen is that of push and pull. Thus,

1) It inhibits the production of FSHRH/FSH.

2) It initiates production of LH-RH/LH.

3) It initiates production of PRH/LTH.
2. Action on CNS:— It acts on the CNS to induce behavioural oestrus in the female.

3. Action upon Reproductive Tract:— The actions of estrogen on reproductive tract are many and have been summarized below.

1) Prolonged administration causes involution of ovary because of its inhibitory activity upon ant. Pituitary.

2) In animals, particularly in bitches administration of estrogen after breeding does not allow conception to continue. It does so by imbalancing the progesterone level and thereby disturbance in nidation. However, it self favours nidation in small doses.

3) It causes hyperemia of the female secondary sex organs and then hypertrophy. The edema of tract associated with estrus and even a firmness of the uterus from intercellular uptake of water.

4) It causes swelling, vascularisation and irritaion of the sec. sex. Organs probably by releasing histamine.

5) It causes growth of uterus, fallopian tube, vagina etc.

6) It causes growth and development of endometrial glands.

7) It causes growth, hyperemia and hypertrophy of the vaginal epi. Leading to their cornification in bitches.

8) It increases the motility of uterus and fallopian tube which helps in transport of gametes.

9) It potentiates the action of oxytocin and prostaglandin on myometrium for easy excitability by lowering the memb. potential.

10) It causes growth of the duct system of mammary gland.

11) The pelvic structures are relaxed, the pubic symphysis softens, and the general perineal area enlarges under prolonged estrogen effects during pregnancy.

12) In high doses estrogen inhibits the output of gonadotrophins by blocking GnRH output.

13) Estrogen is epithelioitropic hormone thus it favours vasostimulation and general health of the skin. This is why the female has a softer, thinner and more luxuriant skin than the male.
4. Action on other tissues of the body:

1) Affects water metabolism: there is mild increase in retention of sodium and water in the tissues.

2) Affects the CNS: creates desire for mating.

3) Affects nitrogen metabolism: there is increased nitrogen retention by the tissues leading to increased protein synthesis (anabolic effect). This property was once exploited for increased meat production.

4) Affects fat metabolism: there is increased fat deposition. It causes increased blood cholesterol level which is well marked in chicken.

5) Affects calcium metabolism. There is increased calcium retention, leading to its increased deposition on bones. This is well marked in laying birds where the serum calcium almost doubles with the approach of estrogentic phase.

6) It causes fusion of long bones and thereby puts a check in their longitudinal growth that is why the females of the same breed are shorter than their corresponding males in whom fusion of the long bones occur a little late.

7) It affects the secondary sex characters in females: Skin becomes thin and glossy with development of glaze in the eyes.

8) It initiates sexual receptivity.

9) It may be responsible for the release of prostaglandin (PGF2α) from both non-gravid as well as gravid uterus at parturition.

10) It stimulates ductal growth in mammary gland.

11) It causes secretory activity in oviduct.

Positive and negative feedback agent: Estrogen can act as a positive feedback agent as well as a negative one. During the proestrus phase of the estrus cycle, the progressive increase in estrogen secretion by the developing follicle stimulates increased GnRH secretion and sensitizes the adenohypophysis to the action of GnRH. The result is a sudden and massive increase in LH secretion which culminates ovulation.

PROGESTERONE:

The main source of progesterone is the luteal cells of the corpus luteum. (theca lutein and granulosa lutein of CL). Although it has been isolated from adrenal cortices and placenta its main physiological source remains the CL. A number of progesterones are available in market.
The progesterone acts synergistically with estrogen in several physiologic functions including growth of uterine and mammary glands.

The addition of two more carbons 20 and 21 at position 17 gives rise to pregnane, the precursor of the progestins.

All steroids have a common cyclo-pentano-perhydro-phenanthrene nucleus.

Pregnan having both methyl group plus an ethyl side chain, is the conceptual precursor of C-21 steroids. Other than these natural progesterones there are a few synthetic progestorones e.g. Norethidrone, Nor-ethynodrel. In addition to these synthetic, there are a number of oral progestenal agents have been used in veterinary practices.

1. MAP (6-methyl-17-acetoxy progesterone)
2. CAP (6-chloro-6-dihydro-17 acetoxy progesterone)
3. MGA (Megesterol acetate)
4. OMPA (dihydroxy progesterone acetophenide)

Hormone synthesis and release: The progesterone synthesis and release is same as to estrogen. The normal effects of progesterone are seen only after the target tissue has been subjected to a period of estrogen stimulation. This priming by estrogen leads to a synergistic effect.

Progesterone is transported in blood by a binding globulin (strongly bound to transcortin). Progesteron secretion is primarily stimulated by LH.

When the sex steroid enter in to the target cell it performs its functions

1. Entry of steroid hormone into target cell: Steroid hormones are lipid soluble and diffuse through cell membrane to cytoplasm without depending upon a transport system.

2. Binding to specific receptors in target cell: A target cell has an inactive cytoplasmic receptor with a high affinity for a particular steroid which becomes an active site after binding.

3. Translocation to the nucleus: The steroid receptor complex migrates into the nucleus where it attaches to a particular area of the chromosome.

4. Binding of steroid-receptor complex to nuclear acceptor site. Once bound, certain genes are then activated or depressed so new RNA can be formed.

5. Formation of new RNA: The target cell increases synthesis of RNA with transcription of mRNA.
6. De induction of steroids:— This occurs by metabolism if steroid is modified to a non-active form or it could be recycled.

Physiologic functions of progesterone:—

1. Action on Hypothalamo-Hypophyseal axis:— It inhibits secretion of gonadotropins and hence till the level of progesterone in circulation remains high estrus and ovulation does not occur.

2. Action on ovary and reproductive tract:—
   a) It is primarily a pregnancy hormone and its deficiency may lead to abortion.
   b) In small amounts it facilitates ovulation.
   c) It causes differentiation of endometrium. The endometrial tissues and the glands primarily acted upon by the estrogens undergo further growth and start secretion.
   d) It makes the uterus suitable for nidation and growth of newly formed zygote.
   e) It brings about secretory changes in the endometrial glands to secrete uterine milk.
   f) It causes growth of secretory alveoli in the estrogen primed mammary glands.
   g) It increases electrical potential difference across the membrane of myometrium and there by prevents easy excitation and reduces uterine motility.

3. Metabolic effect:— It causes retention of water & sodium, chlorides etc. by the target tissues.

4. Progesterone produced by CL/Placenta may be essential for pregnancy maintenance due to its ability to inhibit T- lymphocyte cell-mediated responses involved in tissue rejection.

5. The psychic effects of progesterone favour maternal behaviour in the female such as nest building. The physiological half-life of progesterone is only 22 to 36 minutes in cow which means that a constant secretion is essential to maintain the circulating level. It is important to recognize that the actions of progesterone often occur in synergism with estrogen and often require estrogen priming.
Clinical Applications:–

1. Progesterones are given to prevent abortion in females which prone to abortion as a result of insufficient secretion of endogenous progesterone.

2. The most common use in birth control pills for woman to prevent LH surge and subsequent ovulation.

3. Synthetic progesterone to synchronize the oestrus cycle of Cow. E.g. Melengestrol acetate (MGA).

4. Continues administration of MGA inhibits LH surge, which prevents ovulation but allows development of ovarian follicles.

Prostaglandins:–

Nobel Laureate Von Euler, in 1934, coined the name prostaglandin (PG) for a substance found in human semen. The PGs are rapidly metabolized and serve more as local hormones which act on tissue near the site of their formation. The PGs 1st isolated from accessory sex glands fluid and name given prostaglandins because of their association with the prostate gland. Unlike other hormones, prostaglandins are not localized in any particular tissue. The PGs are involved in control of blood pressure, lipolysis, gastric secretion, blood clotting and other related physiologic processes including renal and respiratory function. The PGF2 is natural leutolytic agent that terminates the luteal phase (corpus luteum) of the estrous cycle and allows for initiation of a new estrous cycle in the absence of fertilization as well as in terminating early pregnancy.

The so-called classic PGs are PGE and PGF have been detected in circulating blood. These two PGs are closely related often exert opposite effects. PGE are generally vasodilators and PGF2 is potent vasoconstrictor. PGE causes shunting of renal blood flow. The PG are pro-inflammatory.

The antipyretic and analgesic effects of aspirin and other drugs are due to their ability to inhibit the synthesis of prostaglandins from arachidonic acid. As well as the anti-inflammatory effects of steroids due to interference in prostaglandin synthesis.

Chemistry:– All PGs are 20-carbon unsaturated hydroxy fatty acids with a cyclo-pentiane ring at Cg-C12. The Arachidonic acid, an essential fatty acid is the precursor for PGs that are most closely associated with reproductive processes namely PGF2α and PGE2. The PGs are named according to the structure of the five membered ring with a subscript indicating the degree of unsaturation of the side chains. The PGF and PGE differ only in a ketonic or hydroxyl group at C-9. Both have hydroxyl group at C-9 and C-15. The PGF was found to be soluble in phosphate (PO4) and PGE soluble in Ether.
Prostaglandins in at least Six Parent Compounds and numerous metabolites exhibit a wide variety of Pharmacological effects.

**Prostaglandins**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Effects</th>
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<tr>
<td>PGE2 and PGF2α</td>
<td>Induction of labor, abortion and destruction of corpus luteum.</td>
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<tr>
<td>PGA1</td>
<td>Gastric secretion inhibition.</td>
</tr>
<tr>
<td>PGE1 and PGE2</td>
<td>Bronchial dilatation.</td>
</tr>
<tr>
<td>PGA1</td>
<td>Vasodilatation and diuresis.</td>
</tr>
<tr>
<td>PGE1</td>
<td>Inhibition of platelet aggregation.</td>
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**Metabolism of PGs** :- Biosynthesis of PGs, thromboxanes, & leukotrienes are generated from arachidonic acid. The leukotrienes are generated through the action on arachidonic acid & are primarily involved in inflammatory processes. The thromboxanes & PGs result from the action of Cyclo-oxygenase on arachidonic acid. Two of these products, thromboxane and prostacyclin are very short lived and donot appear in circulation. The classic prostaglandins PGE and PGF have been detected in circulating blood.

PGF2α is synthesized and released in a pulsatile mode beginning approximately 14 days after ovulation. The estrogens may play a key role in initiating PGF2α synthesis. Decon. facilitate release of PGF2α.

**Transport of PGF2α** :- PGF2α must pass either via the general circulation to reach the ovary or to be transferred from utero-ovarian vein to the ovarian artery.

**Physiologic Functions** :- Prostaglandins regulates several Physiologic and Pharmacologic Phenomena, viz. contraction of smooth muscles in reproductive and gastro-intestinal tracts, erection, ejaculation, sperm transport, ovulation, formation of CL, parturition and milk ejection and ovulation in ewe and cow.

**Prostaglandins in Luteolysis** :- Leutolysin is produced by uterus when pregnancy has not occurred and finally causes regression of the corpus luteum, may be PGs. PGF2α may causes luteolysis by constricting the Utero-Ovarian Vessels and causing ischemia and starvation of luteal cells. The PGs may act by 1) interfering directly with progesterone synthesis. 2) Competing with LH for the receptor site. 3) Destroying LH receptor sites.

PGF2α stimulates contraction of the Uterus, dilates blood vessels and has no luteolytic action. PGF2α stimulates contraction of Uterus, aids in sperm...
transport in male and female causing constriction of blood vessels and has luteolytic properties in domestic animals. It is responsible for regression of CL, may induce hypoxia, which in turn leads to luteolysis. PGs are used to regulate breeding in cows and mares and in abortion of cattle. The trade-names of these compounds are Lutalyse and Estrumate for cow and prostin for mare.

**Regression of Corpus Luteum:** PGF$_2$α initiates regression of CL in large domestic species. The process of regression of CL is due to an inherent luteolytic mech. During the period of diestrus the endometrium/endometrial glands produce PGF$_2$α which on absorption in to Uterine vein which is reabsorbed counter currently by ovarian artery brings about vasoconstriction reducing the supply of blood to the CL which undergoes lysis. As well as PGF$_2$α inhibits adenylate cyclase enzyme for production of cAMP which accelerates the conversion of cholesterol to progesterone leading to fall in progesterone formation.

**Maintenance of Pregnancy:** If CL is not maintained during early pregnancy, abortion will occur in all domestic animals. So the maintenance of pregnancy in these animals is inhibition of secretion of PGF$_2$α in a pulsatile form because PGF$_2$α is luteolytic in nature.

**Ovulation:** The PGF$_2$α induces follicular and ovarian contraction. Thus the pressure on the follicle from which within and out increases leads to rupture of follicle and ovulation occurs.

**Parturition:** PGF$_2$α causes uterine threshold to oxytocin leads to contraction of myometrium which helps in expulsion of fetus in parturition.

**Superovulation:** Shedding of more number of Ova in uniparous animals is known as super Ovulation. A luteolytic dose of PGF2α increases the proportion of ovulatory oestrus.

**Synchronization of oestrus:** PGs are used to synchronize estrus for artificial insemination. The treated animals showed ovulatory oestrus within 2-4 days post-treatment.

**REFERENCES:**


