For Vet Professionals only
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Role of Ecbolics in Improving Reproductive Performance in Bovines

Reproduction plays a pivotal role in successful dairy production. The post-partum period is the most critical period in bovines as they undergo tremendous amount of physical and hormonal changes. A complete anatomical and functional re-organization of the organs involved in the reproductive process are important physiological aspects of the postpartum period, particularly-

- Return of uterus to its pre-pregnancy levels
- Re-epithelialization of endometrium
- Recovery of regular ovarian activity

These events are aimed at ensuring that uterus re-attains the right conditions for next gestation. In particular, the re-surgence of proper uterine contractility is of fundamental importance. The physiological events that take place during the early postpartum period are of special interest in the light of a possible next conception and pregnancy. The first and main function of uterine contractions during the first hours and days after calving is to expel the uterine contents, which include both foetal membranes and lochia.

Uterus and its Layers

Broadly, the uterus consists of three layers of tissues Endometrium, Myometrium and Perimetrium **(Fig-1)**.

A) Endometrium: The innermost layer is the endometrium which lines the lumen of the uterus and consists of a layer of lining columnar pseudostratified or stratified epithelial cells and underlying connective tissue formed by *Stratum compactum* and *spongiosum*.

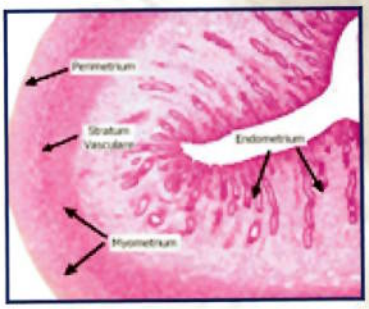

Fig-1: Three layers of uterus *viz.* endometrium, myometrium and perimetrium

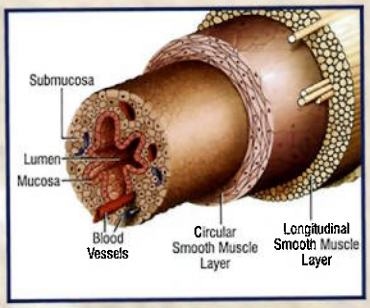

Fig-2: Circular and Longitudinal layers of myometrium separated by *Stratus vasculare*

B) Myometrium: The myometrium consists of a thick inner circular and thin outer longitudinal layer of smooth muscle, separated by *Stratum vasculare* **(Fig-2)**. The longitudinal muscle fibers are parallel and the circular muscle fibers are concentric to the longitudinal axis of the uterus. The *Stratum vasculare* consists of blood vessels and bundles of nerve fibers.

C) Perimetrium: The outermost layer of uterus is the serosa which is vascular and is a continuation of the broad ligament.

There is hypertrophy and hyperplasia of uterine smooth muscles with advancing pregnancy. By end of gestation, the size can increase up to three to five fold of the non-gravid state. The myometrium of uterus is involved in the uterine contractions during and after parturition.

Physiological Phases of Uterine Contractility

Uterine contractibility is divided into different phases:

Phase- 1: Myometrial Activation

As the term approaches, the uterus becomes activated in response to uterotropins, such as estrogen. This phase is characterized by increased expression of a contraction-associated

proteins, CAPs (including myometrial receptors for prostaglandins and oxytocin), activation of specific ion channels, and an increase in connexin-43 (a key component of gap junctions). An increase in gap junction formation between adjacent myometrial cells leads to electrical synchrony within the myometrium and allows for effective coordination of contractions.

Phase- 2: Stimulatory Phase

Following activation, the "primed" uterus can be stimulated to contract by the action of uterotonic agonists, such as the stimulatory Prostaglandins E_2 and $F_2\alpha$ and Oxytocin.

Phase- 3: Involution

Involution of uterus after delivery occurs during phase- 3 and is mediated primarily by Oxytocin.

Nervine Control over Uterine Contractions

Uterine smooth muscles are innervated by the sympathetic nervous system. The postganglionic sympathetic nerves innervates the myometrium originate from the last thoracic and the first lumbar segments of the spinal cord. They travel *via* the hypogastric nerve to the pelvic plexus, where the preganglionic nerves synapse with the so-called short postganglionic neurons supplying the uterine muscle. The smooth muscles cells of the uterus contain both α (excitatory) and β (inhibitory) adrenoceptors. Stimulation of the myometrial cells by the postganglionic nerve fibres is mediated by noradrenaline which acts mainly on α-adrenoceptors in the bovine uterus. Stimulation of the β-adrenoceptors is done by adrenaline.

Role of Uterine Contractions

Parturition

- Parturition is characterized by increase in myometrial activity or, more precisely, a change in the myometrial contractility pattern from "contractures"(long-lasting, low frequency activity) to contractions" (high intensity, high frequency activity), resulting in effacement and dilatation of uterine cervix.
- Parturition is an interesting biological process in the sense that the uterus that was quiescent during the entire pregnancy starts contracting and cervix that was tightly contracted relax sufficiently to allow the passage of the young one to the world outside the mother's womb, passing through the birth canal.
- At the beginning of stage-1 of calving **(Fig-3),** uterine contractions occur approximately once every 15 minutes and increase in frequency to about once every three minutes by the end of this stage. These contractions are not readily noticeable externally and should be differentiated from the abdominal contractions that occur in the stage-2 of calving. Each uterine contraction results in slight breakdown of the connection between placenta and uterus.

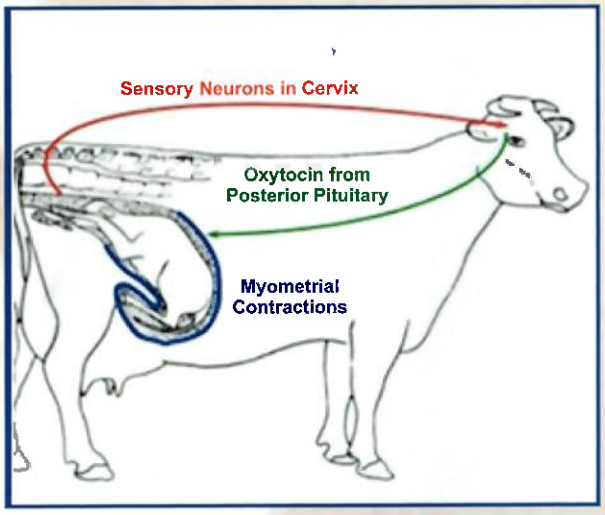

Fig-3: Myometrial contractions in Cow in labour

Removal of Placental Membranes

- After the expulsion of calf, the next step is the shedding of placental membranes. During stage-3 of calving, the attachments of the placenta and foetal membranes to the uterus break down and are expelled. Following delivery of the calf, uterine contractions continue and decrease gradually over the following several days.
- Cows have a bicornuate uterus and the placenta of the cows histologically is of the synepitheliochorial type, meaning that there are five tissue layers between the maternal and foetal circulation during pregnancy. Based on the distribution and arrangement of allantochorionic villi, the bovine placenta can be classified as cotyledonary placenta.
- The allantochorionic membrane makes intimate connection with the uterine wall at areas where finger-like structures or villi form outgrowths, called cotyledons. These groups of villi interdigitate with crypts of specialized areas of the uterine endometrium, called caruncles. Together these contact areas of cotyledons and caruncles are called placentomes. There are approximately 120 functioning placentomes in a pregnant bovine uterus **(Fig-4).**
- Because an intimate connection of the uterus and the allantochorion membrane is only possible at the site of the

placentomes, intercaruncular endometrium is not attached but only apposed to the intercotyledonary parts of foetal membranes. Therefore, separation of foetal parts of placenta only takes place within the placentomes. Purely because of this type of connection and concomitant enzymatic processes, a certain amount of time is needed amount of time is needed for placental expulsion. Typically, these membranes are expelled by cow by 8 -12 hours following calving.

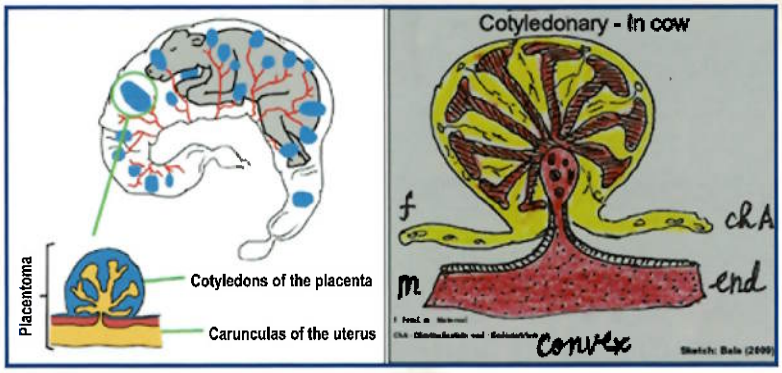

Fig-4: Cotyledons of foetus and caruncles of cow together forming placentome

- Intervention to remove placental tissues from a newly-calved cow should be avoided, as damage to uterine lining may occur as a result of manipulation. Placental maturation is an important part of separation process that happens due to changes in endocrine profile during peripartum period. Other events include separation of cotyledonary villi from maternal caruncular crypts as a result of exsanguination of foetal portion of the placenta, and distortion of placentomes induced by uterine contractions.
- Cases in which shedding either exceeds a period of 12 or 24 hours after calving are usually considered as placental retention (retained foetal membranes/RFM) with a pathological background, in which numerous factors can be involved.

Uterine Involution

- Postpartum period starts immediately after calf birth, and it represents the first part of the puerperal phase, during which a very intense period of uterine involution takes place. Involution is defined as the process by which the tubular genitalia shrink to reverse the hypertrophy that occurs as a result of pregnancy. During involution, the size of the uterus diminishes and both the myometrium and endometrium are restored, so that uterus will be prepared for next conception.
- After parturition cow experience regular well-coordinated contractions in uterus similar to calving. The normal bovine uterus shows a progressive decrease in contractility over time postpartum. By 24 hours post calving the frequency, amplitude and duration of myometrial contractions decrease by over 50% of contractility that was present at 6 hours postpartum. If foetal membranes are retained, contractility remains at about 80% of what it was at 6 hours postpartum to promote detachment.
- Uterine contractions decreases slowly after parturition lead to discharge of debris, fluids and compression of vasculature which ultimately resume its shape, size and biometry. The involution is completed within 5 to 7 weeks, during which a series of physiological processes take place.
- During involution, besides the morphological changes of the endometrium, the size of the uterus also markedly decreases. The greatest size reduction in normal cows occurs during the first few days after parturition.
- Diameter of the previously gravid horn halves by 5 days postpartum, its length halves by 15 days.
- Weight of the average uterus decreases from 8-10 kg at calving to <1 kg at 25-30 days and 0.75 kg at 50 days (**Fig-5**).
- Involution occurs in a decreasing logarithmic pattern, with reduction in rate of involution between days 4 and 9 post-partum, followed by an acceleration of the rate of involution between days 10 and 14, and gradual slowing until the process is complete.
- Bovine uterus returns to its pre-gravid state by about 25 days post-partum, but completion of entire involution process takes between 25 and 50 days after parturition.
- The mechanical activity of uterine smooth muscle plays an important role in the process of uterine involution. During postpartum period, spontaneous uterine contractility increases intrauterine pressure which helps to eliminate fluid and debris from the uterine lumen. This is part of innate defence mechanism and is possible because of contraction of circular and longitudinal muscle layers of myometrium and it contributes to first line of defence together with professional phagocytes.

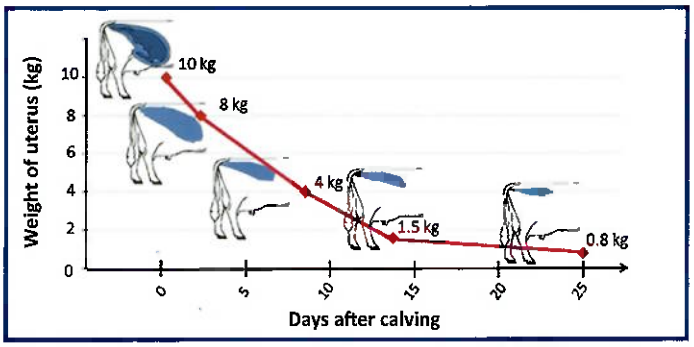

Fig-5: Reduction in size of uterus in postpartum cow

- Physical propulsion generated by contraction of circular and longitudinal muscles helps in evacuation of uterine fluid and debris. Contraction of myometrial muscle fibers plays a major role in expulsion of lochia which continues for 14 to 23 days postpartum.
- Nutrition plays an important role in myometrial contraction. Macro and micro minerals are essential for improving immunity, maintaining mineral homeostasis and improving uterine involution. **MINFA GOLD** is a scientifically formulated mineral mixture that minimizes periparturient complications and improves uterine involution.
- Poor myometrial contractions result in delayed clearance of fluid, debris and bacteria, predisposing the cow to postpartum uterine disease. Therefore, uterine involution and myometrial tone are very important factors contributing to uterine defence.
- Some factors responsible for decreased myometrial contractility include lack of exercise, lack of regular suckling, and hypocalcemia, resulting in reduced uterine clearance, accumulation of lochia and increased risk of bacterial infection.

Uterus Contractile Events in Postpartum Cows

a) Events of the first day postpartum with special emphasis on the first 8 hours

- Although after expulsion of foetus, abdominal straining efforts disappear, frequent and strong uterine contractions remain, showing a high degree of regularity. The physiological purpose of this activity is dislodgement of cotyledons from their corresponding caruncles and subsequent expulsion of foetal membranes. In fact, this represents the final, post-calving stage (stage-3) of parturition process.
- Frequency of individual contractions at this time, has been reported to vary between 12 and 30 per hour and shows a decrease during the consecutive hours after expulsion of calf.
- Decline in frequency until 2 hours after calving was shown to be linear, with mean values ranging between 14 and 19 contractions per hour. Amplitudes during first two hours after normal calving have been found to vary between 20 and 40 mmHg.
- During first few post-calving hours, contractions are propagated in a tubocervical direction. Main function of the strong, tubocervically propagating contraction waves occurring during this period, appears to be expulsion of the placenta.
- The contractility markedly decreases after shedding of the foetal membranes, within first 8 hours postpartum.

b) Events during the second day postpartum

- Uterine contractions become weaker on second day, but they are still present and still appeared to be propagated in a tubocervical direction.
- Uterine contractions generally diminished rapidly, with a major decline between 12 and 24 hours after calving, and with very little spontaneous contractility left at 48 hours.
- Maximal amplitudes of 50 to 80 mmHg, and contraction frequencies varying between 8.6 and 40 per hour, have been measured in cows showing retained foetal membranes (RFM) with significantly higher uterine activity at 48 hours in cows with RFM than in animals without RFM.

Factors Affecting Uterine Contractility

Several factors and conditions affect the contractions of uterine muscle cells.

1) **Availability of intracellular calcium:** It is one of the essential components and, therefore, plasma calcium levels are of clinical importance in postpartum animals. The pattern of myometrial contractions changes upon expulsion of calf, but contractions do remain and show a regular pattern, characterized by powerful and frequent individual pressure cycles. However, if a cow suffers from milk fever, due to severe reduction in the blood Ca^{2+} concentration during immediate post-calving stage, uterine contractions reduces markedly. Flaccid uterus can be palpated and in such cases intrauterine pressure changes. Hypocalcemia has also been associated with higher incidence rate of RFM. Substantial evidence suggests that in cows with subclinical hypocalcemia, involution may be delayed.
2) **Nursing and milking:** Direct effect of milking or nursing on uterine contractility during puerperal period is controversial. Few studies find no differences in uterine contractility patterns of cow with presence or absence of calf, even if calf was allowed to lick or suckle her mother

Fig-6: Nursing and milking have positive impact on postpartum uterine contractions and involution

whereas some studies has observed a positive effect of nursing and have also reported increased uterine activity after milking or nursing or even only because of seeing their calves nearby (**Fig-6**). The negative effect of calf removal on the release of oxytocin most likely contributes to decline of uterine contractility in postpartum cows.

3) **Uterine relaxants:** Uterine relaxants or tocolytic agents can temporarily reduce uterine contractions. These medications are beneficial during obstetrical aid in parturient animals with abnormal foetal presentations, foetal oversize or uterine displacements or torsion. It is often used during caesarean sections to exteriorize the pregnant uterine horn in ruminants. There is a reduced uterine contractility in cows where uterine relaxants are used.

Consequences of Abnormal Uterine Contractility

The uterus of early postpartum dairy cow is of special interest in view of its role in subsequent conception and pregnancy. As reproduction is an important factor in the economy of cattle farm, earlier the causes of reproductive disorders are recognized and eliminated, better are the chances for improving reproductive performance and, indirectly, economic effectiveness. The reproductive efficiency of a dairy herd is generally defined in terms of calving interval. The length of the calving interval influences milk yield and affects culling rate as a result of reproductive disorders. Inappropriate uterine involution prolongs calving-to-conception days, overall affects calving interval. Immediately after calving uterine involution starts, preparing the genital tract for a subsequent conception. Puerperal disorders in this early period may cause an extension of complete uterine involution and may lead to delayed resumption of ovarian activity, causing prolonged calving to conception intervals and increasing production costs at the farm. Uterine smooth muscle activity plays an important role in expulsion of uterine contents, clearing of its cavity and in the reduction of uterine size. These processes, however, can be perturbed, resulting in puerperal disorders, such as retained foetal membranes (RFM), or endometritis.

Veterinary Ecbolics

Ecbolics are medicines that increases uterine contractions and uterine involution process. In bovine practice, several ecbolic drugs are used during puerperal period. Such treatments are still often based on tradition, or practical experiences of Veterinarians, rather than on the proper indication for treatment and the documented knowledge of their immediate and long-lasting effects on uterine functions. The ecbolic or uterotonic drugs, used in bovine practice during postpartum period, include prostaglandin F2α, oxytocin or ergot alkaloids.

Oxytocin

Oxytocin elicits myometrial contractions directly by stimulating myometrial oxytocin receptors. An additional, indirect pathway may also exist, in which occupation of endometrial oxytocin receptors lead to release of prostaglandins (PG), which on their turn act on myometrium by a paracrine route. A treatment with 30 IU of oxytocin exerts a positive effect on uterine contractility up to the second day postpartum. A positive effect of oxytocin becomes less evident during 4^{th} to 6^{th} day post partum. The half-life of oxytocin is very short resulting in short duration uterotonic effect.

$PGF_2\alpha$

Prostaglandin $F_2\alpha$ (PGF2α), is luteolytic and has uterotonic effects. The uterotonic effect is mediated by G-protein-coupled cell surface receptors and depends on presence of these receptors in different regions of the uterus. There are two types of receptors, FP, selective for $PGF_2\alpha$ and EP_2 selective for PGE_2 which when activated cause contraction and relaxation of the uterus respectively. It has been shown that the fundus of the uterus has abundant FP receptors that upon activation cause myometrial contractions. The cervical region has more EP_2receptors that facilitate myometrial relaxation and cervical dilation. During gestation there are higher numbers of relaxant receptors (EP_2) and lower numbers of contractile receptors (FP) in the uterus to maintain uterine quiescence. At the onset of labor, the number of FP receptors increase to help with the onset of contractions, and to maintain contractions during the postpartum period. The action of $PGF_2\alpha$ depends on the specific FP receptors in the postpartum bovine uterus to initiate myometrial contractility to facilitate uterine clearance and involution.

Methylergometrine

Ergometrine is a naturally occurring alkaloid found in ergot (*Claviceps purpurea*). It is classified as a water-soluble lysergic acid derivative and has ability to stimulate uterine contractions. The maleate salt (ergometrine maleate) exhibits greater stability than the free base and is the usual form in which the alkaloid is used in medicinal products. It is used in veterinary medicine in the control of postpartum uterine haemorrhage, removal of fluid from atonic uteri, to prevent prolapsed

uteri and judiciously in terms of timing to aid in suturing the uterus after caesarean section or in replacing an averted uterus.

Dose regimens are:

- Cows and Mares: 2 to 5 mg/animal (intravenously or intramuscularly)
- Ewes, Goats and Sows: 0.5 to 1 mg/animal (intramuscularly)

NEXBOLIC containing methylergometrine injection is an effective ecbolic with proven efficacy. Ergometrine maleate is rapidly absorbed (after oral administration and by intramuscular injection) and rapidly effective about 10 minutes after oral dosing and 7 minutes and 1 minute after intramuscular and intravenous injections, respectively. The action persists maximally for about 1 hour and gradually lessens over a period of several hours. Elimination appears to be principally via the bile after metabolism in the liver.

Herbal Preparations

The oral administration of herbal preparations with proven ecbolic and restorative actions also appears to be safe and effective option, both therapeutically and prophylactically. **PROSHE** is a polyherbal oral liquid with proven efficacy as ecbolic and is used for managing retention of foetal membranes and improving uterine involution.

Reproductive efficiency is under tremendous thrust and focus in cattle rearing. The post-partum period is critical for maintaining healthy animals, profitable farm and prosperous farmer. Any pathology occurring during this period impacts the reproductive and productive efficiency of cows. A more holistic and dynamic approach is needed during peri-parturient period to ensure healthy postpartum in cows. Postpartum pathological conditions like retention of placenta, uterine diseases, metabolic disorders and nutritional imbalances delay the uterine involution and contribute to poor reproductive efficiency in dairy cattle. Uterine contractions play significant role in uterine involution. Therapy that increases the frequency, duration and strength of uterine contractions in the postpartum period help in enhancing uterine involution, resulting in improved reproductive performance. Usage of ecbolics have been accepted globally in improving uterine involution, minimising postpartum haemorrhages, preventing retention of foetal membranes and improving reproductive efficiency.

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