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Incomplete dilation of cervix in large animals: A review

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Abstract
Cervix dilation, which happens soon before parturition, is an essential component of successful vaginal birth of young children. Cervical dilatation is a complex process that results from hormonal modulation, an inflammatory response, and the breakdown of collagen by enzymes. It is third most common cause of bovine dystocia and typically a disorder of ruminant cervix.
Incomplete cervix dilation may be occurred due to weak myometrial contractions, uterine inertia (Primary or secondary) or hormonal deficiency. Cases of incomplete cervix dilation can diagnose by clinical sign with progressive prolonged first stage of labor, per-rectal examination or per-vaginal examination. Oxytocin, cytokines, prostaglandins, estrogen, relaxin, nitric oxide, neurons, and other substances are all involved. Failure of cervical dilatation due to changes in the cervical ripening mechanism or insufficient uterine contraction might cause complications in fetus delivery.
For the management of cervical dilatation failure, cervical massage, cervicotomy or a number of hormones, chemicals have been used but caesarean section is only available best tool for management.

Keywords: Cervix dilation, parturition, myometrial contraction

1. Introduction
For successful vaginal delivery of fetus or young one, cervix dilation plays an important role. In animals, cervix dilation is a complex process involving hormone modulation, inflammatory processes, and collagen enzymatic degradation.
Among the different causes of maternal dystocia in farm animal species, incomplete cervical dilation is one of the important causes (Noakes *et al*., 2009) which is typically a disorder of ruminant cervix. Whereas, incomplete dilation of cervix is third most common cause of bovine dystocia (Jackson, 2004) [18]. As per the Weldeyohanes *et al*. (2020) [46], incomplete cervix dilation cases more frequently observed in cattle and less common in buffaloes (Purohit *et al*., 2011) [35] The root cause of this pathology is mainly associated with the alteration in the cervical ripening mechanism, insufficient uterine contraction, hormonal imbalances. The failure of the cervical rings to relax completely in the event of parturition also leads to retention of fetus in utero and causes dystocia like conditions.
Cervix of cow is more cartilaginous in compare to other farm animals so if it is not dilated at the time of first stage of parturition it may cause sever dystocia (Sloss *et al.,* 1980) [38]. Cervical priming is a gradual dilation and softening of the cervix in large ruminants during the first stage of parturition (Jackson, 2004) [18]. Maul *et al.* (2005) observed that during the initiation of cervix dilation inflammatory network play key role. Incomplete cervical dilatation in multiparous cows may be linked to hypocalcemia-induced uterine inertia (Noakes *et al*., 2009).

2. Occurrences
Out of all the causes of dystocia, 17 per cent dystocia occurs due to cervical origin in cattle (Wehrend *et al*., 2003) [44] while 38 per cent in beef cattle (Sloss *et al.*,1967) [39]. Purohit *et al.* (2011) [35] found 5.1% incidence of dystocia due to incomplete cervix dilation in cattle and buffaloes.

2.1 Anatomy of cervix
The cervix is a sphincter-like structure that protrudes into the vaginal canal caudally. The cervix is a fibrous organ made up mostly of connective tissue and a few smooth muscle bundles that run longitudinally and transversely (Word *et al*., 2007) [49].
Generally, the cervix in cattle is characterized by a thick wall and constricted lumen. Tissue of cervical region is made up of 3 layers *i.e*., a mucosal layer, muscular layer and serosal layer.

Serosal layer is outermost layer whereas muscular layer is middle later consist inner circular and outer longitudinal layer followed by inner layer *i.e.,* mucosal layer, which consist of epithelium and underlying stroma. Fitzpatrick *et al.* (1977) [10, 11] studied detailed anatomy of cervix in which cervical stroma is made up by ground substance associated with proteins like collagen, elastin and reticulin. Ground substance involved hyaluronic acid, dermatan sulfate, chondroitin 6-sulphate, heparin sulfate, chondroitin 4-sulfate, and keratin sulfate. Cellular element composed of mast cells, fibroblasts and wandering cells. Among the fibers, collagen appears to be numerous. In cervix, elastin is present in only small amount while collagen is randomly oriented, dense or closely packed and embedded in high molecular weight proteoglycans complex while (Ward *et al.,* 1968) [43].

There are different types of collagen fibrils such as collagen type I, type III or type IV within the cervix and these are differed into cervix of non-pregnant and cervix of early pregnant cow. As per the Fitzpatrick *et al*. (1977) [10, 11], Glycosaminoglycans (GAGs) act as cement or binding substances whereas, collagen fibrils have affinity to bind with GAGs so, collagen fibrils strongly bind to anionic group of GAGs. There is several molecules found in the extracellular matrix of cervical connective tissue which results into biochemical alteration with their interaction and these all responsible for the functional properties of cervix. Cervical remodeling occurs due to interactions of several endocrine factors and these biochemical alterations (Fitzpatrick *et al*., 1977) [10, 11].

Collagens and GAGs play key role into cervical remodeling during the parturition. As the process of parturition begins, changes start to occur in concentration of collagen and GAGs. There is reorganization of collagen fibrils just before parturition which results into to make the cervix easily distensible and the dynamic of reorganization of fibrils is commonly known as cervical ripening. Dynamic of cervical ripening can be divided into two stages- first is gradual cervical ripening and second is final cervical ripening. During last month of pregnancy gradual cervical ripening occurs which is utmost prerequisite for a successful and final cervical dilatation followed by second stage (*i.e.,* final cervical ripening) which happen during the parturition process (Winkler *et al.,* 1999 and Malmstrom *et al*., 2007) [48].

Stromal cells, fibroblast and smooth muscle cells plays an important role during this period of cervix dilation (Breeveld-Dwarkasing *et al.,* 2003) whereas, Stromal cells secreted Matrix Matello Proteinases (MMPs). However, during final cervical ripening inflammatory cells also act as additional source of MMPs secretions (Stygar *et al.,* 2002) [40]. These MMPs are secreted as proenzymes and after proteolytic cleavage they become activated (Hulboy *et al.,* 1997) [17]. In gradual ripening different types of MMPs are involved *i.e.*, MMPs-1(Fibroblastcollagenase), MMP-2 (Gelatinase-A), MMP-8(leukocyte collagenase), MMP-9(Gelatinase-B) etc. (Malmstrom *et al.,* 2007 and Osmers *et al.,* 1992). MMP-1, MMP-2 and MMP-8 play role into cleave fibrillar collagen types I, II, III while collagen types IV and V cleaves by MMP-9 (Nagase *et al.,* 1999 and Hulboy *et al.,*1997) [31, 17]. During cervical remodeling, activity of MMPs is tightly regulated by some inhibiting factors like β2 macroglobulin and tissue inhibitors of Matello Proteinases (TIMPs) (Nagase *et al.,* 2006) [32]. During the cervix dilation digestion process also occurs which results in to changes in collagen organization pattern and cause from digestion of densely packed, large bundles of collagen fibrils (Bryant *et al.,* 1968) into smaller bundles, more dispersed, and randomly oriented collagen fibrils. However, Breeveld-Dwarkasing *et al*. (2003) reported that during the process of gradual ripening collagen is not completely digested.

At the beginning of parturition, hyaluronic acid (HA) act as the predominant GAGs in the cervix because in cervix, high hyaluronan content attracts water molecules and it causes increase hydration which ultimately led to dispersion of collagen fibers within cervix. Due to high content of hyaluronan there is increase into space between collagen fibrils, collagen denaturation and hydration with the ending of first stage of parturition (Breeveld-Dwarkasing *et al.,* 2003 and Maillot *et al.,* 1976) [28]. These all alteration bring structural changes and tensile property of cervix at the time of final dilatation that results it in more extensible (Kelly *et al.,* 2005) [21].

Process of final cervical ripening and inflammatory process are very much similar which is mainly characterized by presence of proinflammatory cytokines, granulocytes such as neutrophils and eosinophil's (Tornblom *et al.,* 2005 and Wehrend *et al.,* 2004) [41, 45]. In the pregnant animals, the placenta and extraplacental membranes (gestational tissues) has been said to be sources of a large number of cytokines, chemokines and related factors (Bowen *et al.,* 2002) [4] and in these gestational tissues both proinflammatory and anti-inflammatory cytokines were expressed. Erik van Engelen *et al*. (2009) [42] studied the expression of TNF-α and cytokine expression in bovine cervical tissue at different day of pregnancy and they reported that cytokine expression with the completion of gestation periods, there is increase in the expression of IL-8, IL-1β and IL-10 however, expression of IL-6 remained unaltered. These expressions increase mainly at parturition, compared to day 185 pregnancy. While with the beginning of parturition expression of TNF-α decreased. Among the proinflammatory cytokines, IL-8 plays a very important role in during cervical softening. When compared to non-pregnant cervix, IL-8 production and secretion are considerably increased in pregnant animal cervix at term, and IL-8 concentrations in the cervical and lower uterine section increased with cervical ripening (Sennstrom *et al*., 1998 and Winkler *et al*., 1998) [37, 47]. Increases in leukocyte infiltration and MMP concentrations in the tissue are linked to an increase in IL-8 during cervical ripening (Osmers *et al*., 1995 and Winkler *et al*., 1999) [48]. Anti-inflammatory cytokines IL-10 and IL-4, in addition to proinflammatory cytokines, play a role in cervical softening.

3. Causative factors

Dilatation of ripened cervix is mainly regulated my myometrial contractions (Lindgren, 1973) [26] so if there is weak myometrial contraction, it may become causative factor for incomplete cervical dilation and finally causes dystocia. It may be either because of primary uterine inertia or secondary uterine inertia.

Mee (2004) reported that hypocalcemia is the main causal factor of primary uterine inertia and other then hypocalcemia, other factors like hyposelenaemia, hypomagnesaemia also causes primary uterine inertia. Old age, debility, lack of exercise and pre-term calving and twin calving can also influence the myometrial contractions (Mee, 2004). Some hormones like estrogen, relaxin, prostaglandin play important role in myometrial contraction and cervix dilation so, their imbalance or failure of sufficient hormone secretion also

cause uterine inertia.
Noakes *et al. (*2009) concluded that secondary uterine inertia also is one pf the factor of incomplete cervix dilation which may be occured because of prolonged dystocia, malposition and twin calving.
Different hormones like progesterone, estrogen, oxytocin, relaxin etc play important role into cervix dilation. Among the hormonal factors including steroids, prostaglandin and relaxin at term, it has been seen that imbalance in secretion or concentration of any hormones result into impaired cervix dilation. If progesterone activity increased during parturition, it decreased myometrial contractility and myometrial gap junction development (Da Fonseca *et al*., 2003) [7]. Mahendroo *et al*. (2012) [27] studied dynamic of cervix dilation in mice and found that deficiency of 5 α-reductase and increased concentration of progesterone with in the cervix causes increases tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) (Leppert *et al*., 1992) and hence inhibits collagenolysis.
If progesterone concentration is higher so it causes down regulation of prostaglandin production with inhibition of development of calcium channels and Oxytocin receptors so it finally inhibited myometrial contractions and incomplete cervix dilation (Da Fonseca *et al.*, 2003) [7].
Some metabolic factors also affect the cervix dilation, among this fat mobilization is important factor because it can diminish magnesium availability and calcium mobilisation, it can cause uterine inertia and cervical dilatation failure. (Anon, 2006) [1].

4. Clinical signs
History plays an important in diagnosing the case. Non-progressing prolonged first stage of labor is the key sign of diagnosing the case of incomplete cervix dilation. In which owner of animal complained for non-progressing labor since long time. Generally, in natural parturition, cervix became continuous with vagina and is not palpable per rectally but, in case of cervical non-dilatation, cervix can be palpate through per rectal examination (Purohit *et al.*, 2011) [35].
For conforming the case per-vaginum examination also performed. On per vaginum examination generally whole hand can pass through cervix in complete dilated cervix but in case of incomplete cervix dilation, only 1 or 2 fingure may be inserted through cervix and sometimes parts of fetus or fetal membrane can be palpated (Jackson *et al*., 2004) [18].

5. Management
The animals are examined for other signs of parturition like ligament relaxation and colostrum filled in udder should present. Manual attempts or feathering is very simple and easy way to dilated cervix in which we have to inserting 1 or 2 fingers (or the hand with fingers pointed in conical shape) and massage slowely so it can be made to dilate the cervix. But in case of bovine, it is not often possible to dilate the cervix because bovine cervix consists of many annular rings (Purohit *et al.*, 2011) [35].
If the fetus is present in the birth canal but cervix is not dilated properly so, sometimes cervix can dilated through gentle traction over long period. If the fetus is live and fetal membranes are intact but cervix is closed, then animal may be left for 30 minutes and reexamined. Purohit *et al.* (2011) [35] suggested that if the legs of a putrefied dead fetus are present in the birth canal but the fetus cannot come out because of incompletely dilated cervix so, partial cervicotomy should performed instead of caesarian section.

5.1 Manual method
5.1.1. Cervical massage
It is a simple and easily performed method in which by using sodium salts of carboxy methyl cellulose (CMC) or lukewarm water we massage the cervix for 15 minutes at hourly intervals for three times at least which may result into smooth and soft cervix with complete cervix dilation.

5.1.2. Cervicotomy
If the legs of putrefied dead fetus are present in the birth canal but fetus cannot come out due to incompletely dilated cervix so it is suggested to performed partially cervicotomy instead of caesarian section (Purohit *et al.,* 2011) [35]. In this procedure we made a cut at 1 or more places in cervical rim which dilate the cervix at the point.

5.2 Hormonal method
There are many hormones which directly or indirectly affect the parturition and dilation of cervix.

5.2.1. Prostaglandins
Fuchs *et al.* (2002) [13] suggested that prostaglandins play an important role in cervical softening which may be suspected that at the term their increased levels in the uterus, cervix and fetal membranes have been observed in cattle.
Cervical softening may be induced by local application of PGE2 during clinical obstetrics operations (keirse *et al.,* 1993) [20]. Duchens *et al*. (1993) [8] and lavoir *et al*. (1996) [24] reported that after endocervical administration of PGE2, the cervix of heifers undergoes softening because PGE2 has both proinflammatory and anti-inflammatory action (Kelly, 1992) [22]. Proinflammatory actions of PGE_2 with IL-8 show synergistic action which further attracts and degranulate the invading neutrophils however, anti-inflammatory action of PGE_2 involved in maintenance of pregnancy (Kelly, 1996).
Misoprostol is a synthetic prostaglandin. Azavi *et al.* (2011) [2] reported first successful use of misoprostol in a local breed of cows suffering from incomplete cervical dilatation. He inserted 1 mg of misoprostol (Cytotec, Searle Pharmaceuticals Ltd, UK) in partially dilated cervical canal of cow and found good results.
Carbol *et al.* (1987) [6] inserted Dinoprostone in rat and shown that the cervix can undergoes structural changes similar to those preceding normal delivery with use of Dinoprostone.

5.2.2. Estradiol
It is mainly used in the cases of partially dilated cervix because it induces collagenase activity and is involved in collagen remodeling. Estradiol also responsible for stimulate expression of Oxytocin receptor (OTR) in endometrium as well as in cervical epithelial cells so it further causes release of prostaglandins which is also responsible for powerful myometrial contraction so it is obvious that high estrogen concentration is very essential for completion of cervical ripening process.

5.2.3. Relaxin
Cervical dilatation may also be induced by relaxin which causes remodeling of connective tissue in several mammalian species, especially in pigs. Hartung *et al.* (1995) [16] found if we injected porcine relaxin on cervical tissue of late pregnant heifers so it is suggestive that effect of relaxin is mediated by presence of receptors.
Effect of relaxin also affected their route of administration. If

it is injected intramuscularly so it causes cervical dilatation in late pregnant heifers whereas, if relaxin is injected intravenously in late pregnant heifers so doesn't results in earlier. Thus, effect of relaxin is also affected with timing and method of administration which play an important role to induced cervical remodeling in ruminants.

5.2.4. Valethamate (Epidosin)
It is anti-cholinergic agent and quaternary ammonia compound with peripheral action similar to atropine enabling cervical dilation.
In large animal it is commonly use to dilate the cervix during parturition with dose rate of 40-50mg intramuscularly.

5.2.5. Oxytocin
Oxytocin has specific effect on uterine smooth muscles. It binds with the specific receptors, present in myometrium and this binding stimulate the smooth muscles contraction and uterine motility which further promoting cervix dilation.
In large animal oxytocin uses @ of 75-100 IU intramuscularly.

5.3. Chemical method
5.3.1. β - adrenergic agonist
Some β - adrenergic drugs have been used for cervical dilatation by virtue that they cause relaxation of entire genital tract. In this, Isoxuprine at the doses of 200-300 mg intravenously or 0.3 mg intravenously Clenbuterol have been suggested.
Although results are not promising always and moreover, they also delay the parturition process (Tocolysis).

5.3.2. Hyaluronan
Hyaluronan content of cervix increases at term to facilitate cervical ripening by attracting water molecules, increasing collagenase activity, decreasing collagen concentration, affecting function of Polymorphonuclear cells (PMN) and relaxation of cervical smooth muscle. Increased hyaluronan synthase expression and the subsequent increase in hyaluronic acid (HA) is a distinct feature of cervical ripening and dilatation (Kelly *et al.*, 2005) [21] in mouse at the term. In normal tissue, high molecular weight (HMW) hyaluronic acid is the predominant form and regulates cell behavior (Alaniz *et al*., 2009) While low molecular weight (LMW) hyaluronic acid is angiogenic (Joddar *et al.*, 2006) [19].

5.3.3 Other combinations
Brijesh *et al*. (2018) reported the combination comprising mainly four drugs is affected in treatment of incomplete cervix dilation, which included injection Valethamate @ 80mg intramuscular, injection Dexamethasone @ 40mg intramuscular, injection cloprostenol @ 500mcg intramuscular and injection estrogen @ 10mg intramuscular.

5.3.4 Calcium
Incomplete cervix dilation is may be because of hypocalcemia involved in the pathogenesis, by impairing myometrial contractions of uterus (subsequently causing uterine inertia). Calcium therapy may help in dilating the cervix by increasing uterine contractions and which further results into cervix dilation in cattle.

5.4. Surgical management
Caesarean section is indicated if it does not respond to medical treatment with hormones and calcium borogluconate (Roberts, 2004) [36]. Along with incomplete cervix dilation, if there is evidence of fetal hypoxia or hyperactive movements of the fetus and expulsion of the meconium so, urgent intervention is indicated and hysterectomy should perform immediately.
There are different available surgical approaches for bovine caesarean section *i.e.*, the standing left paralumbar celiotomy, standing right paralumbar celiotomy, recumbent left paralumbar celiotomy, recumbent right paralumbar celiotomy, recumbent ventral midline celiotomy, recumbent ventral paramedian celiotomy, ventrolateral celiotomy, and the standing left oblique celiotomy. Each has its own advantages and disadvantages.

6. Conclusion
The process of cervical dilation in large animals is poorly understood and the etiological factors behind to poor cervical dilatation during parturition are not exactly known. The therapies which are currently available are not satisfactory or their role is also not fully evaluated. Caesarean section is a one of the best tools for management of cervical dilatation in cattle as well as in sheep if other treatment fails to resolve.
There are multiple hormones like oxytocin, prostaglandins, estrogen, relaxin etc. are involved in the process of cervix dilation and other then hormones some factors also involved, which are cytokines, nitric oxide, neurons etc. and it is occurred due to change in hormonal concentration, various enzymatic and inflammatory mechanism (Gahlot *et al.*, 2017) [14].
Cervix dilation is a two-stage process started during last months of pregnency to just before or at the stage 1 of parturition and incomplete cervix dilation in large animals can manage by combination of hormonal drugs like combination of velethamide bromide with prostaglandins and calcium etc.

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