CONSIDERATIONS OF INTRA-UTERINE THERAPY IN GYNAECO-CLINICAL PRACTICE

Optimum fertility potential is necessary in animals for economic dairy entrepreneurship. Infection of genital organs is an important cause of impaired fertility. Low-grade endometritis due to infections and secondary inflammations constitute major uterine pathology. Additionally, uterine affections like placental retention, pyometra are clinically important. Prompt therapeutic regime and attention towards hygienic husbandry practices helps to restore fertility.

Local drug application is possible by intra nasal, intra ocular, intra pharyngeal and even by intra gastric routes. Intra uterine route is also very similar to local drug administration. Indications, procedure, prerequisites, effectiveness of the treatment and drug considerations of intrauterine route have been discussed in this paper.

Scope of I/U therapy:

Intra-uterine (IU) therapy is practiced because a high concentration of antibiotic can be achieved in the infected uterus and antibiotic can be present in therapeutic concentration in the uterine inflammatory exudates. Also, after absorption of the antibiotic into the circulation, there is continuous return of drug to the endometrium for a period of time. No major damage occurs to tissues other than affected organ on attempting IU therapy.

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In case of retention of placenta, repeat breeding, pyometra, coital infections and metritis, the infection is present inside the uterus and genital passage. The infection may spread in the body via bloodstream. However, the uterine infections are more at local site and the drugs placed in uterus have more action at local site. Thus IU therapy helps to remove the infection completely from uterus and it can prevent toxic hazards, which can occur due to spread of toxins from uterus.

Open cervix facilitates the way for intrauterine therapy. Drug placed in uterus is absorbed in better way from the endometrium of the uterus especially after parturition and these drugs gives moderate concentration in the blood and helps to cure the infection. Good results can be obtained to cure all infections if IU therapy used along with parental injections of antibiotics.

From clinical point, the clinician must logically answer following questions before attempting intrauterine therapy.

- What is the current uterine environment?
- Which pathogen is most likely the cause of infection?
- Which antibiotic is most likely to be effective?
- How much should be the drug concentration at the site of infection?
- Whether local (IU) route will be ideal for the treatment?
- What are the alternatives to the antimicrobial treatment?

Precautions during IU therapy:

If IU route is adopted one must consider how often and for how long period antibiotic should be administered and what dose or what volume should be employed. Forceful infusion of douching fluid in excess volume into non-pregnant uterus of heifer may cause damage to the uterus. Larger volume of liquid will completely fill the uterine lumen and will create pressure on uterine walls. The drug solution may enter in fallopian tubes and in the pelvic cavity. As a consequence of douching with pressure, fluid may escape in the
peritoneal cavity resulting in peritonitis. Also if large volume of drug is infused in uterus, the drug may appear in milk of treated animals and milk from such treated animals will not be useful for human consumption for 72 hours.

The administration of drug by IU route is only possible when os-cervix is open. Os-cervix is slightly dilated on the day of oestrus and largely dilated after parturition for 3 to 4 days. Intrauterine therapy in empty animals is only possible when the animal is in oestrus stage, as cervical dilatation is present. After foetal expulsion and during early period of purperium suitably intrauterine therapy can be carried out. Partial opening of cervix is present in some of the uterine affections.

Cervical affections causing hindrances or kinked appearance of cervix limit use of intrauterine therapy. In no case drug should be administered in uterus by forceful dilatation of the cervix. Unless cervix is open and patent through its entire course, intrauterine therapy should be avoided. Never insert glass/steel pipette forcefully through the cervix for intrauterine therapy.

**Technique of IU therapy:**

While attempting intrauterine therapy, strict aseptic precautions are necessary and always avoid use of contaminated hands, pipettes, artificial insemination guns, plastic sheaths, etc. Professional risk to the handler should be negligible. Animal is well restrained in the travis and peri-vulval parts are cleaned with soap water or potassium permanganate solution (1: 1000). Operator should clean his hands and arms thoroughly.

The solid preparations like antibiotic powder boluses, pessaries are directly installed in uterus by passing well-lubricated gloved hand through vagina and open cervix. These preparations are placed in uterine horns. This is only possible after parturition for 3 to 4 days.

Powdered form of antibiotics or chemicals is diluted either in distilled water or in normal saline for intrauterine use. IU therapy with liquid preparations is attempted very cautiously. Well-lubricated left hand is passed through rectum and the cervix is secured well. Sterile catheter / pipette is directed into vagina by right hand and with
the help of left hand tip of the pipette is directed in forward and upward motion towards the os-cervix. Generally an obstruction is encountered at the first annular fold of the cervix. If so, slowly withdraw the catheter, rotate it and then again pass it forwards to overcome the problem. With continuous gentle forward pressure on the catheter by and gradual rotation, spiral cervical canal can be traversed. The tip of pipette should be placed against the folds of cervix and liquid infusion is made without actual passing pipette into uterus. In sheep and goats, os-cervix is located by using a well-lubricated vaginal speculum and the intrauterine therapy with liquid preparations is carried out.

**Indications for IU therapy:**

Intrauterine therapy is indicated in common pathological and accidental conditions of genital affections. Retention of placenta is basically due to failure of the villi of the foetal cotyledons to detach themselves from maternal crypts of caruncles. It may be due to infection of uterus during pregnancy, which does not allow the separation. Repeat breeding is the most common cause of infertility. Repeat breeder animal fails to settle even after three consecutive services or inseminations. Infectious cause of repeat breeding necessitates IU therapy.

There are various uterine affections in which intrauterine therapy is attempted. Endometritis leads to repeat breeding and is basically due to uterine infection and secondary inflammation. Pyometra is accumulation of pus in the uterus due to infection and inflammation. Perimetritis and parametritis mean the inflammation of the serosa and uterine ligaments respectively. Sclerotic metritis is caused by severe chronic metritis that has caused by complete destruction of endometrium and fibrolytic changes in uterine wall. Septic metritis is the infectious condition is observed within ten days after parturition and is associated with uterine atony and inertia. The pathogenic organisms and their toxins are absorbed into the circulation producing severe general symptoms associated with septicaemia, toxaemia and pyemia.
Salpingitis is more common in cows and buffaloes than mare. Organisms found in oviducts are similar to those found in infected uterus. Intrauterine infusion in large volumes cures the oviductal infection. Post partum bleeding due to capillary haemorrhage on the surface of cotyledons or excessive handling during placental removal is accidental and needs proper attention. Uterine tear or rupture of gravid uterus (accidental) and caesarean section (surgical intervention) requires antibiotics for rapid healing of the uterus through intrauterine therapy.

**Uterine microflora:**

Uterus normally harbor variety of bacterial strains. The inhabitant organisms are normally non pathogenic but may become pathogenic under adverse health conditions. Bovine uterus is the ideal site for bacterial multiplication. Trauma, inter-concurrent infections, failure of local immune mechanization leads to bacterial multiplication. Common bacterial agents, which lead to infertility and uterine pathology, are Corynebacterium pyogens, Escherichia-coli, Streptococci, Staphylococci, and Pseudomonas. Generally infection starts with streptococci dysagalactia then staphylococci, diptheroides, corynebacterium pyogens and lastly anaerobic bacteria aggravate infection.

Steroid hormones regulate the potential pathogenecity of microorganisms. During the oestrogenic phase of oestrus cycle, there is increased blood flow to the uterus, increased mucus discharge and intensified PMN cell activity and hence infection is restricted. Progesterone favours immunosuppression and lymphocyte inhibition, which intern flourishes pathogenicity of microbes.

**Uterine defense mechanism:**

Uterus has its own natural system of defense mechanism to fight against microorganisms. The uterine defense mechanism is effected automatically through continuous degeneration and regeneration of superficial endometrial layer, chemically by mucus secretion from the endometrial glands and immunologically through the action of both humoral antibodies and polymorphonuclear cells.
Polymorphonuclear cells. Blood monocytes and tissue macrophages are regarded as professional phagocytes in cellular defense against pathogenic microorganisms. Uterine defense mechanism resists the bacterial multiplications.

Superficial endometrial layer is a temporary layer, which continuously undergoes degeneration and regeneration even normally during oestrus cycle. The phenomenon is physiological and cyclic. However, deep endometrial layer is permanent and always proliferates to replace the degenerated superficial layer.

A leukocyte response predominated by polymorphonuclear cells, commences two days after calving. During first 15 days of parturition, degenerative inflammatory cytogram and from 20th day of calving for a week ahead regenerative inflammatory cytogram is evident in parturited animals.

Though intrauterine antibiotic therapy is invented to support uterine defense mechanism, the microbial growth inhibition factors also inhibit phagocyte capacity of uterine derived polymorphonuclear (PMN) cells. Hence alternate approach is now available to strengthen natural uterine defense mechanism with use of immunomodulators like E. coli lipopolysaccharides, Oyster glycogen or leukotriene B4 through IU route.

Theoretically, infections should be treated with antimicrobials only until the host’s defense system is adequate to resolve the infection.

**Prerequisites for IU therapy:**

Treatment of any disease condition depends upon correct diagnosis of disease. Diagnosis of etio-pathology in uterine infections is prerequisite for IU therapy. Culture and sensitivity test is always necessary before attempting IU therapy. There is often wide variation in sensitivity of susceptible microorganisms on bacterial strains to any antibiotics.

It has been observed that sensitivity is limited to higher antibiotics in genital infections. This might be perhaps due to undue usage of lower range of antibiotics for various ailments for a considerable period.
Susceptibility profiles can vary between herds and flocks. Susceptibility tests are intended to be a guide for the practitioner, not a guarantee, that an antimicrobial will be effective in therapy. Susceptibility testing can only give an indication of what the clinical activity of the drug will be. The effect of the drug in vivo depends on its ability to reach the site of infection in a high enough concentration, the nature of the pathological process and the immune responses of the host.

Complete siphoning, evacuation, or removal of uterine contents is most important before attempting IU therapy. Squeezing of uterine horns gently or handling of horns provokes uterine discharge, if volume of contents is large. Suction of contents from uterine horns can be possibly attempted in clinical cases.

Attempt of saline irrigation of uterine horns is also considered as standard scientific procedure and is known as douching. Use of antiseptics is preferred for uterine douche. However, failure to remove complete saline from uterus favours the infections for further multiplication. The left over fluid acts as medium for bacterial growth.

IU therapy is practically very similar in major steps like wound dressing. Intra uterine drug administration should be attempted only after best possible cleaning of the site. Simultaneous parental drug administration helps in early clearance of infection.

Drug approach for IU therapy:

Once the diagnosis is confirmed, then the drug of choice is selected. Generally, the drugs are classified under four main categories as allopathic, ayurvedic, homeopathic and chemicals. Ayurvedic and homeopathic drugs are administered by oral route only. Allopathic drugs can be used by IU route. However, certain acids and chemicals are also having beneficial effect by IU route. Antiseptics are capable of destroying pathogenic microorganisms but cannot eliminate bacterial spores.

Under the category of allopathic drugs antibiotics are important. In antimicrobial therapy, it is essential that desirable effective level of drug be achieved and maintained for an adequate period of time.
at the site of infection. Rational use of antibiotics for intrauterine infusions always provides fruitful results only when used after carrying out antibiogram and perfect diagnosis of bacterial flora.

Other therapeutic options should be considered prior to antimicrobial therapy. To minimize the likelihood of broad antimicrobial resistance development, where an appropriate narrow spectrum agent is available, it should be selected in preference to a broad-spectrum agent.

The action of antimicrobials can be either bactericidal (Penicillins, Cephalosporins, Aminoglycosides, Bacitracin, Polymixin-B, Trimethoprim) or bacteriostatic (Tetracycline, Chloramphenicol, Lincomycin, Septinomycin, Sulphonamides).

Judicious use of antimicrobials is an integral part of good veterinary practice. It is an attitude to maximize therapeutic efficacy and minimize selection of resistant microorganisms. Indiscriminate use of antibiotics and chemicals for intrauterine infusions for uterine affections leads to

1) Development of bacterial resistance to unsuitable antibiotic.
2) Unnecessary irritation of the site of drug administration.
3) Increase in treatment cost and unnecessary financial taxation.
4) It indicates no proper attempt of diagnosis.
5) It also fails to give results of recovery and the condition continues.

It is obvious that single antibiotic therapy may not be effective for complete elimination of pathogenic organisms. It would be novel approach to use drug combinations for avoiding uterine affections after screening the microbial sensitivity. Intrauterine treatment should be inclusive of different drugs for which the bacterial strains are sensitive hence combination of antibiotics is essential.

The choice of the right antimicrobial needs to take into account pharmaco-kinetic parameters, such as bioavailability, tissue distribution, apparent elimination half-life, and tissue kinetics to ensure the selected therapeutic agent reaches the site of infection. Duration of withdrawal times may be a factor in choosing suitable products.
Uterine affections can be treated by systemic therapy, intrauterine therapy or combination of both approaches. For complete elimination of infection, drug administration should be carried out by both intrauterine and systemic routes.

Preventive strategies, such as appropriate husbandry and hygiene, routine health monitoring, and immunizations, should be emphasized. Diseases must be controlled to reduce the need for antimicrobial use and they can only be controlled successfully by preventive medicine.

**Common drugs for IU:**

Acriflavin is a slow acting antiseptic nontoxic and germicidal. Adrenaline is a sympathomimetic drug, which is principally used as local haemostatic and is commonly combined with local anaesthetic because of its local capillary constriction action. Bismuth subnitrate exerts sedative desiccant action. Boric acid is non-irritant and non-poisonous antiseptic. Iodine is antiseptic, disinfectant, resolvant and is good oxidizing agent but it is irritant and therefore retards healing. Hydrogen peroxide solution is having an antimicrobial and deodorant action. On use of hydrogen peroxide, there is rapid production of oxygen, which causes an expulsion of pus and cell debris.

Almost all the available antibiotics have been used for the treatment of uterine affections. Prostaglandin has also been used by IU route. There is limited evidence, if any that the IU infusion of antimicrobials with or without lytic enzymes and oestrogen has any beneficial effect in the treatment.

**IU therapy after parturition:**

Adequate selenium and vitamin E nutrition during last term of gestation will enhance udder health and aid in minimizing the incidence of retained placenta in postpartum animals. Ensuring adequate pre-calving nutrition, particularly protein, is of paramount importance. This will enhance the passive transfer of antibodies from high quality colostrum to the neonatal calf and has been proven to provide health benefits throughout the life of the animal.
Regularly treatment of retained placenta consists of manual removal of the placenta by gentle traction and separation from maternal cotyledons. Intrauterine therapy after parturition is carried out with objective of increasing uterine blood circulation and also to create antiseptic environment for avoiding secondary bacterial infections.

Sulphonamides in solution or boluses are often placed in uterus to aid prophylaxis of treatment of genital infection locally in uterus but as these are insoluble they may tend to settle in the apex of horn. Urea is often incorporated in preparations as a sulphonamide adjuvant. High concentration of urea increases action of sulphonamide by increasing their solubility, inhibiting their actions with proteins and neutralizes certain antagonists of sulphonamide activity. IU use of sulphonamides may result in residues in meat and milk when solutions are infused in uterus of dairy animals for 24 – 48 hours.

Post partum bovine uterus is essentially with anaerobic environment, which makes amino glycoside drugs completely in effective, as these antibiotics require oxygen for their activity.

IU therapy for Low-grade endometritis:

Intrauterine infusions in repeat breeder animals have been a subject of considerable controversy with reports of success as well as failures. In case of repeat breeder animals microbial pattern assessment and blood biochemical profiling is must. Treatment effective for elimination of all aerobic and anaerobic infections may not be effective in improvement of conception rate unless blood metabolic fuels are optimum in cyclic non-breeder animals.

Uterus is susceptible to infection in luteal phase but it is resistant to infection in follicular phase. Therefore treatment is more effective near the time of oestrus. The drugs causing severe inflammatory reaction in uterus should be avoided because uterus controls the length of oestrus stage and either increases or decreases the length of oestrus cycle.

Lugol’s iodine is most commonly used under field condition to treat endometritis. Besides the antiseptic activity, Lugol’s iodine causes local
irritation of endometrium, releases prostaglandin and regresses ovarian corpus luteum. Intern by reflex actions, gonadotrophins are secreted for induction of cyclicity.

**Controversial side of IU therapy:**

IU therapy is being regularly used by the field practitioners and is also widely adopted under research trials. The therapy is proved successful for the treatment of gynecological and obstetrical cases. However, its use is always controversial because of treatment failures.

There are some disadvantages of IU therapy over other routes of administration. It is not easy to carry out IU therapy especially when dosing is required two or three times daily, although indwelling catheters may to some extent overcome this problem. There is every possibility of introduction of other bacteria into uterus during manipulation, if proper aseptic precaution is not taken. There may be every possibility of toxic local effect of antibiotic on the endometrium.

The necessity for IU medication is controversial. Systemic administration of antibiotics is reported to have better advantage than local administration. Use of antiseptics, disinfectants, antimicrobials or antibiotics and even manual removal of placenta may inhibit uterine leukocyte phagocytic activity for several days.

The local administration of antibiotic may not be always preferred in the treatment of genital tract. It has been shown that systemic administration of antibiotic achieves tissue concentration of drugs in all areas of genital tract, where as IU infusion results in incomparable concentration only in endometrium and urinary secretions. Furthermore, a diseased endometrium considerably impairs the absorption of locally infused antibiotics. It is observed that osmolarity of the vehicle and pathology of uterus (types) also affects drug transport in endometrial tissue.

Antimicrobials, antibiotics and antiseptics having irritant action on endometrium leads to severe endometrial damage. It is proved that higher concentration of oxytetracycline and Lugol’s iodine causes
severe, diffuse, sub epithelial and perigrandular haemorrhage and severe oedema. These changes are more severe in superficial zones than that of the dipper zones. All the changes of haemorrhage and oedema will subside after 72 hours of IU therapy.

For decades, endometritis in animals has been treated with intrauterine infusion of a bewildering array of substances. This is now receiving closer scrutiny. Although infusion of antimicrobials may rid the uterus of bacteria, there is no evidence that it eliminates the endometrial inflammation or restores the affected animal to fertility. Indeed, many preparations routinely administered into bovine uterus are known to be detrimental to uterine tissue. Increased concern about milk and carcass residues, alongwith poor or uncertain results, should discourage intrauterine therapy as a routine approach to management of bovine endometritis. In the rare cases in which systemic signs of illness are seen, systemic administration of antimicrobial is indicated.

Conclusions:

The best approach proposed for intrauterine therapy will include undertaking of culture and sensitivity testing of uterine discharge, complete siphoning of uterine contents and attempts of saline irrigation of uterine horns and attempt of intrauterine drug administration with simultaneous systemic therapy.