**Mitigating Abortion in Nellore Ewes Caused by *Brucella melitensis* Using Oral Medroxyprogesterone Acetate Therapy**

**ABSTRACT**

**Aim:** Prevention of abortion in the Nellore ewes caused by the Brucella Melitensis

**Study design:** A total of 90 pregnant ewes were included in the study from November 17, 2024, they were administered a 7-day course of oral medroxyprogesterone acetate tablets at a dosage of 10 mg.

**Place and Duration of Study: Mr**. Ramana Reddy Farm, Ramapuram, Annamayya District, Andhra Pradesh during 2024-25

**Methodology:**  *Brucella melitensis* is the primary etiological agent of brucellosis in small domestic ruminants.   *B. melitensis*remains endemic and associated with an extensive negative impact on the productivity and reproductivity of flocks prevalent in most sheep-raising regions in the world. *B. melitensis* infection causes abortion, stillbirths and the birth of weak offspring, and occasionally epididymo-orchitis in goats and sheep. The treatment with antibiotics is costly and protracted due of the intracellular growth of the pathogen. Even after treatment, recurrence of infection is very common. Vaccination with  *B.melitensis* is second alternative but consumes lot of state budget but calls for number of veterinary personal and the availability of the vaccine. The next best alternative is to study the efficacy of long acting synthetic progesterone. The effect of medroxyprogesterone acetate, a synthetic progesterone hormone, was studied in 90 threatened ewes with 10 mg of medroxyprogesterone acetate for 7 days orally and continuously. The infection was detected with the Rose Bengal Precipitation test and further confirmed with Enzyme Linked Immunosorbent Assay.

**Results:** Out of 90 treated sheep, 87 (96.6%) ewes had normal lambing.

**Conclusion:**The reason for the profound reduction in the abortion incidence may be due to anti-inflammatory, anti-oxidative, and anti-microbial effects and replenishment of inhibited progesterone, necessary for the maintenance of pregnancy.

**KEY WORDS**

Abortion, *Brucella melitensis*, Ewe, Medroxyprogesterone acetate

**1.INTRODUCTION**

Several infectious and non-infectious causes can lead to pregnancy loss in small ruminants, such as sheep and goats. Zoonotic illnesses are among the infectious causes of pregnancy loss in small ruminants and they can result in severe clinical illness and abortion in humans (Agerholm, 2015). *B. melitensis*, *Campylobacter* species, *Chlamydia abortus*, *Coxiella burnetii*, Leptospira species, *Listeria monocytogenes*, *Salmonella* species, *Yersinia pseudotuberculosis*, *Aspergillus* species, bluetongue virus, border disease virus, Cache Valley virus, caprine herpes virus-1, *Neospora caninum*, and *Toxoplasma gondii* are among the major causes of infectious abortion in small ruminants. Toxic plants, poisons, dietary inadequacies, and environmental variables are among the less common non-infectious causes of abortion in small ruminants (Agerholm, 2015).

According to McDermott *et al.* (2013), brucellosis has consistently been regarded as one of the most economically significant zoonosis globally, with numerous economic implications attributed to human, animal, and wildlife disease. Since animal brucellosis not only results in production losses (From abortion, stillbirth, sterility, a longer calving interval and lower milk yields), but also acts as a barrier to trade, countries engaged in intensive livestock farming are particularly affected economically, despite the fact that the disease's importance to public health is recognized globally (Akakpo *et al.* 2009).

Despite the fact thatpreventive immunizations are the next best line of defence against  *B.melitensis* in sheep and goats, many developing nations do not practice this because of a lack of funding, a shortage of veterinary and para-veterinary personnel, and the availability of an adequate and effective vaccine. While some nations have utilized other vaccines, such as the *B. suis*S2 and *B. melitensis*M5 vaccines, the Rev-1 vaccine is typically used in small ruminants. Serological testing is hampered by the Rev-1 vaccine, especially when administered subcutaneously. However, lambs aged 3-5 months when given sub- conjunctively minimized the situation. *Brucella suis* vaccine strain 2 infects goat trophoblast cells (GTCs), replicates efficiently, and induces apoptosis through endoplasmic reticulum (ER) stress, contributing to abortion. Pharmacological chaperones modulating ER stress influenced its replication, with GRP78 and the IRE1 pathway promoting proliferation. The infection altered hormone secretion and steroidogenic gene expression, shedding light on Brucella-induced abortions via ER stress and reproductive endocrinology (Wang *et al.* 2016).

A lengthy course of antibiotics is typically used to treat brucellosis in humans, sometimes involving the combination of two or more medications. Relapse rates are said to be high with monotherapy. Various antibiotics might be suggested based on the patient's age, pregnant status, and condition. Streptomycin resistance exists in the Rev-1 vaccination strain. If brucellosis treatment is not sufficient, relapses may occur, usually within three to six months.Surgical intervention may occasionally be required for localized foci (Spickler 2018).

In general, the treatment of animal brucellosis has not been fully successful because of the intercellular localization of *Brucella* organisms within phagocytic cells of the reticulo-endothelial system in lymph nodes, liver, spleen, mammary glands and reproductive organs. Therefore, the *Brucella* organisms are protected from antibodies, complement and antibiotics (Rossetti, 2022).

In the adult patients with uncomplicated brucellosis, the doxycycline-aminoglycoside combination remains the preferred treatment, with doxycycline-rifampin and doxycycline-cotrimoxazole serving as alternative regimens. Additional oral regimens, including quinolones, may also be considered as alternatives. For patients under 8 years of age, a six-week regimen of cotrimoxazole combined with rifampin is recommended, while gentamicin for 5 days followed by cotrimoxazole for six weeks may serve as a suitable alternative (Alavi and Alavi 2013).

Other explanations for treatment failures include incorrect choice and dose of antibiotics or insufficient duration of treatment and/or improper routes of administration. In addition, the high cost of therapy, long duration of treatment, antibiotic residues in milk and meat and, in many cases, failure to cure udder infections have led to the general conclusion that treatment has no role in the control of animal brucellosis (Radwan *et al.*, 1992).

An exhaustive data analysis of the different therapeutic regime in humans indicate that of the 11,747 records identified through the database search compared with standard therapy ie., doxycycline + rifampicin, rifampicin + tetracyclines, doxycycline + trimethoprim, doxycycline+ quinolones, streptomycin + tetracyclines were less efficacious. Doxycycline+gentamicin ranked the best in efficacy followed by triple therapy (Doxycycline+ rifampicin+ aminoglycoside) and third is and the third is doxycycline + streptomycin. But all do these have very long therapeutic regimes, do have many side effects and the cost is also high (Huang *et al.* 2024).

The next alternative and viable approach is to investigate the potential use of suitable hormones. Among these, medroxyprogesterone acetate, a synthetic long-acting oral hormone, emerges as a candidate based on the different earlier findings.

Since progesterone is known to be necessary for the initiation and maintenance of pregnancy, Jingjing Ren *et al.* (2021), showed that an infection with *Brucella abortus* lowers progesterone levels in pregnant mice by preventing the placenta from producing progesterone. In mice infected with *B. abortus*, progesterone therapy dramatically decreased the release of inflammatory cytokines in the serum, macrophages and trophoblasts, which decreased placentitis and improved pup survivability. Mechanistically, progesterone inhibits NF-kB activation, which lowers the inflammatory response. Additionally, progesterone therapy inhibited the growth of *B. abortus* in trophoblasts, which is linked to the bacteria's failure to leave the late endosome compartment *in vitro*. Together, it was demonstrated how progesterone therapy may be helpful in preventing placentitis or abortion brought on by an infection with *B. abortus* (Jabbar, 2012).

Moreover, serum progesterone levels in cows and buffaloes with a positive Brucella infection were significantly lower (P<0.05) in infected animals (0.495±0.13 ng/ml) than in the non-infected group (18.468±6.26 ng/ml). The progesterone/oestradiol balance (P/E Ratio), which reached 0.107 percent in the infected group compared to 3.132 percent in the non-infected group, reflects this declined in progesterone concentration (Jabbar, 2012).

The researchers found that progesterone demonstrated bacteriostatic action against gram positive bacteria, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Gaffkyatetragena*, *Bacillus subtilis*, and *Listeria monocytogenes*. However, it did not exhibit antibacterial effects against gram negative bacteria such as *Escherichia coli*, *Aerobacter aerogenes*, *Salmonella paratyphi* and*Proteus vulgaris*, nor against the fungus *Candida albicans*. The study concluded that progesterone's bacteriostatic action was primarily effective against gram-positive microorganisms (Byndloss *et al.* 2020). Hence, the anti-abortifacient activity of medroxyprogesterone acetate might also can be attributed to its direct or indirect activity against *Brucella* organisms.

With this background, an attempt was made to prevent pregnancy loss due to *B*.*melitensis* in 90 pregnant ewes belonging to Mr. Ramana Reddy, Ramapuram, Annamayya District, Andhra Pradesh during 2024-25.

**2.MATERIALS AND METHODS**

**2.1. Experimental material**

Medroxyprogesterone acetate (Deviry® 1mg tablet, Torrent pharmaceuticals Ltd, India) was used in the present study which were procured from local reputed medical shop. One tablet per day per pregnant ewe was orally administered for 7 days.

Mechanism of action of medroxyprogesteroneacetate is similar to naturally occurring progesterone. The mechanism of action of progestin involves binding the progesterone receptor in the hypothalamus, female reproductive tract, and pituitary and inhibiting the secretion of gonadotropin-releasing hormone (Mishell, 1996).  It also has [androgenic](https://en.wikipedia.org/wiki/Androgen) activity and weak [glucocorticoid](https://en.wikipedia.org/wiki/Glucocorticoid) activity. Due to its progestogenic activity, medroxyprogesterone acetate decreases the body's release of [gonadotropins](https://en.wikipedia.org/wiki/Gonadotropin) and can suppress [sex hormone](https://en.wikipedia.org/wiki/Sex_hormone) levels.

**2.2Ewes infected with brucellosis**

A shepherd, Mr. Venkata Ramana Reddy, presented at Sreepathi Veterinary Clinic, Kadapa, reporting recurrent abortion issues in his flock of 120 sheep, with annual abortion rates of 60–70% over the past four years, including the current year, 2024. This year, he observed 30 abortions, predominantly in maiden ewes. Clinical signs included full-term foetal abortions, retained or easily separated placentas, and lambs born alive but dying shortly after birth. Aborted foetuses were covered with yellow serosanguineous discharges and often associated with degenerative placentas. A thick, dark red or yellowish vulvar discharge was noted, persisting for one to two weeks. Pregnant ewes exhibited dullness and pyrexia for 2–3 days prior to aborting either live or dead foetuses. A total of 90 pregnant ewes were included in the study, and starting on November 17, 2024, they were administered a 7-day course of oral medroxyprogesterone acetate tablets at a dosage of 10 mg.

**2.3.*In vitro*anti-bacterial efficacy of medroxyprogesterone acetate**

The *in vitro* anti-bacterial efficacy of the medroxyprogesterone acetate was conducted in the BSL 3 laboratory of Institute of Animal Health and veterinary Biologicals, Karnataka Veterinary Animal and Fisheries Sciences University, Bidar following the standard protocols by Agar Well Diffusion Method, Broth Microdilution Assay and Disk Diffusion Assay (Kirby-Bauer method) (CLSI, 2023). The serial dilution of the MPA was made and the zone of the inhibition was calculated and the MIC as per the standard protocol.

**3.RESULTS AND DISCUSSION**

The results of the present study are presented in Table 1, 2 and 3 as well as Figure 1 and 2.

**3.1.Serological diagnosis**

Prior to administration of the medroxyprogesterone acetate, the ewes were confirmed for the pregnancy and by history of date of mating, abdominal palpation, estimation of progesterone, pregnancy associated glycoprotein, ultrasonographic evaluation. The brucellosis was confirmed by Rose Bengal Precipitation Test by Animal Disease Diagnostic Laboratory,Kadapa, Andhra Pradesh and the same samples were subjected to ELISA Test by Veterinary Biologicals ResearchInstitute, Vijayawada, Andhra Pradesh and found positive for  *B.melitensis* organism**.**It was observed that even after 90 days of completion of the course of medroxyprogesterone acetate, the animals were did not reinfected as per the serological study which depicted that there might be sustained effect of drug might have was continued.

**3.2.Disease pattern studies**

Most animals are believed to contract the infection through ingestion as well as *via* the oronasal and conjunctival mucosa. However, this organism can also be transmitted sexually and through damaged skin. Sheep and goats can remain infected for extended periods. They have the ability to shed *B. melitensis* regardless of whether they abort or carry the pregnancy to term, and reinfection of the uterus and subsequent abortions can happen during prospective pregnancies(Spickler, 2018).

The shepherd replaced the entire stock for the past 4 years but was unable to prevent pregnancy loss due to abortion in sheep. He purchased once lambed sheep but the subsequent lambing season, he observed 70 per cent abortions. His two breeding rams were absolutely free of infection but one young one which was not exposed to breeding was found to be positive. This clearly demonstrates either contact or ingestion of the organism through contaminated shed or grazing land, the flock acquired the infection.

Among the three aborted ewes, two were maiden ewes, while the third was a multiparous ewe in her third lambing. The abortions were likely attributed to a combination of high-intensity infection and elevated oxidative stress during the third trimester. The efficacy of medroxyprogesterone acetate was observed to persist until the last recorded healthy lambing on January 17, 2025, maintaining effectiveness for 60 days.

**3.3.Anti-bacterial activity**

In the present study, the MPS in the different concentrations of MPA did show the antimicrobial activity and MIC was found to be very minimal. This indicates that the MPA did not hadthe antimicrobialactivity and the entire action is attributed to its progesterogenic activity which is in accordance with the study conducted by Jingjing Ren *et al.* (2021). The drug may have the potential to prevent abortion along with the combination with antibiotics and further studies are required in this aspect (Figure 4 and Figure 5).

**3.4.Anti-inflammatory activity**

During bacteraemia, *Brucella*organism enters the placenta through specialized trophoblastic cells located toward the foetal side, between the bases of cotyledonary villi of the placentomes that are involved in phagocytosis of macromolecules, especially extravasated maternal blood. Thus, *Brucella* organism takes advantage of an important physiological mechanism for the trans-placental transport of iron needed by the developing foetus for erythropoiesis to colonize naive targets. From these phagocytic trophoblasts, *Brucella* spreads and replicate into adjacent chorioallantoic trophoblasts (Samartino *et al.*1996). Massive intracellular multiplication induces apoptosis of trophoblasts due to endoplasmic reticulum stress and release of huge numbers of microorganisms into the uterine lumen. Though, the cycles of endocytosis (Or active penetration), intracellular replication and cell death continue.Certain molecular studies demonstrated that *Brucella*-infected trophoblasts secrete pro-inflammatory chemokines such as IL6, IL8, GCP-2 and MCP-1, and hormones prolactin and estrogen, while the secretion of progesterone is inhibited (García-Méndez *et al.* 2019).

In addition to this, Jingjing Ren *et al.* (2021),demonstrated that *Brucella abortus* infection inhibits progesterone levels in the pregnant mouse by suppressing the production of progesterone by placenta. Progesterone treatment reduced the secretion of inflammatory cytokines in serum, macrophages, and trophoblasts of *B. abortus*-infected mice, leading to decreased placentitis and enhancing the pup viability. Mechanistically, this decreased inflammatory response results from inhibition of NF-kB activation by progesterone. Further, progesterone treatment suppresses *B. abortus* growth within trophoblasts associated with an inability of bacteria to escape the late endosome compartment *in vitro*. Collectively, it was illustrated that progesterone treatment might be useful therapeutically in protection against placentitis or abortion caused by *B. abortus* infection.

Jesse *et al.* (2016),analyzed the serum concentration of progesterone and estrogen in the healthy and infected mice with *B.melitensis* and found that progesterone declined by 13 % in infected mice and the progesterone and estrogen ratio increased by 31% in infected mice than healthy ones.

Akihiko Wakatsuki *et al.* (2002), demonstrated that although estrogen increased C-reactive protein and serum amyloid A protein concentrations, medroxyprogesterone acetate attenuates the proinflammatory effect of estrogen.Serum amyloid A (SAA) concentrations have been investigated in diseases of domestic animals. Increased SAA levels have been associated with neonatal infection, bovine respiratory disease, brucellosis, septicaemia and arthritis.

Porter *et al*.(2020), reported that medroxyprogesterone acetate suppressed amyloid- ß degradation in an MMP-9-dependent manner, *in vitro,* and potentially compromised the clearance of amyloid-beta *in vivo*. Amyloid-ß has antibacterial, antifungal, and antiviral properties that are effective against at least eleven species of microbes.

Cows and buffalos positive for *Brucella* infection showed insignificant serum progesterone concentration decrease (P<0.05) in infected animals (0.495±0.13 ng/ml) compared with (18.468±6.26 ng/ml) in non-infected group. This decrement of progesterone concentration reflected on the progesterone/ estradiol balance (P/E Ratio) which reach (0.107%) in infected group compared with (3.132%) in non-infected group (Jabber, 2012).

Medroxyprogesterone acetate may potentially impair immune function by reducing T cell production of interleukin 17 (IL-17) A and interferon-gamma (IFN-γ) through the expression of the aryl hydrocarbon receptor, which may impact some aspects of infection progression. Medroxyprogesterone acetate may be tissue protective by lowering interleukin 17 (IL-17) A and raising interleukin -22 (IL-22). The damaging effects of theimmune response may be mitigated by the protective hormone interleukin 22 (IL22), which is produced by medroxyprogesterone acetate administration. Additionally, medroxyprogesterone acetate may reduce the inflammatory processes and limit the tissue damage seen in certain autoimmune disorders (Fernández, 2016).

**3.5.Anti-oxidative activity of medroxyprogesterone acetate**

The antioxidant system consists of three primary components: glutathione peroxidase, catalase, and superoxide dismutase, which function to inhibit the generation of new free radical species. By neutralizing radicals as they form, scavenging antioxidants, including vitamin E, vitamin C, and uric acid, play a crucial role in preventing oxidative stress. Additionally, preventive antioxidants mitigate oxidative damage by sequestering transition metal ions, thereby reducing their capacity to catalyze free radical formation. Thus, they are mostly proteins by nature, including ceruloplasmin, albumin and transferrin (Chapple1, 997). Assays for biological fluids' total antioxidant capacity were created because these antioxidant defence mechanisms seem to work in concert rather than separately (Miller *et al*. 1993).

In contrast, total antioxidant capacity level was significantly lower in*Brucella*affected patients as compared with controls (p < 0.001). There was no statistically significant difference between the catalase results of the two groups (p>0.05). Oxidative level index was significantly increased in patients as compared with healthy controls (p<0.001) (Tranquilli *et al.* 1995).

Progesterone combined with different antibiotics has a significant effect on chronic endometritis, which can reduce the level of inflammation, increase the thickness of endometrium, improve the level of uterine status and normal menstruation rate, reduce the level of sex hormones and the rate of irregular vaginal bleedingetc. It has a good effect, high drug safety, helps to improve the quality of life (Lan *et al.* 2023).

**4.CONCLUSION**

It is concludedthat administration of medroxyprogesterone @ 10 mg per day orally for 7 days to pregnant ewes, could prevent pregnancy loses to the extent of 70-90% in sheep and goats compared to untreated animals. Theeventual performance may be due to itscombined anti-inflammatory, anti-oxidative and antibacterial actionor may be due to replenishment of progesterone to the deficientpregnant ewes.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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**Table 1: Antibiotic versus hormonal therapy**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Year** | **Population of sheep** | **Abortions before treatment** | **Mode of treatment** | **Abortions after treatment** | **Percentage**  **of abortions** |
| 2021-22 | 120 | 90 | Antibiotics and tonics | 90 | 75 |
| 2022-23 | 120 | 80 | Antibiotics and tonics | 80 | 66 |
| 2023-24 | 100 | 70 | Antibiotics and tonics | 70 | 60 |
| 2024-25 | 115 | 20 | Medroxy progesterone acetate | 3 | 2.6 |

**Table 2: Abortions pattern before and after hormonal treatment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Month** | **Trimester** | **Treatment** | **Number of pregnant** | **Number of abortions** | **Percentage of abortions** |
| October 2024 | Third | Oral antibiotic therapy with doxycycline (100 mg) and rifampin (15 mg/kg) for 15 days | 30 | 25 | 83 |
| November 2024 | Third | Hormonal therapy with medroxyprogesterone acetate 10 mg for 7 days oral. | 38 | 2 | 5.2 |
| December 2024 | Second | No treatment | 10 | 1 | 10 |
| January 2025 | First | No treatment | 20 | 0 | 0 |

**Table 3: Test positive with Rose Bengal Precipitation Test**

|  |  |  |  |
| --- | --- | --- | --- |
| **Details** | **Aborted ewes** | **Breeding rams** | **Healthily**  **lambed ewes** |
| Number of sheep screened | 6 | 3 | 3 |
| Positive | 6 | 2 | 0 |

|  |
| --- |
| **Figure 1: Aborted foetus due to Brucellosis in ewe** |
| Visual search query image |
| **Figure 2: Result of Rose Bengal Test positive for brucellosis** |
| Screenshot_2024-12-06-12-15-20-93_6012fa4d4ddec268fc5c7112cbb265e7 |
| Figure 3: Culture and sensitivity test of *Brucella melitensis* with medroxyprogesterone acetate |
|  |