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Comparative efficacy of intravaginal steroidal and non-steroidal drugs in estrus synchronization in ewes

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Abstract
The study was conducted to compare the efficacy of non-steroidal (Letrozole) and steroidal (Avikesil-S®) drugs in estrus synchronization combined with PGF2α in local ewes. A total of 24 apparently healthy non pregnant ewes were randomly allotted into two groups with 12 each. Ewes in Group I and Group II were inserted with intravaginal Letrozole sponges and Avikesil-S sponges, respectively for seven days and were injected (i.m) with 125 µg of PGF2α at the time of sponge removal. Two proven ram were used for estrus detection and also for mating. The bred ewes were subjected for pregnancy diagnosis on day 30 post mating by ultrasonagraphy. Sponge retention rate was 100% in both the study groups with estrus response rate of 83.33%. The interval to estrus in Group I (89.4±2.24 h) was significantly higher ($p<0.05$) than in Group II (45.59±1.57 h). The duration of estrus between Group I (34.85±1.83 h) and Group II (34.7±1.31 h) did not differ significantly. The conception rate recorded was higher (70.00%) in Group I compared to Group II (50.00%). It was concluded that the Letrozole sponges are as effective as Avikesil-S sponges in estrus synchronization with better conception rate in local sheep.

Keywords: Ewes, estrus synchronization, letrozole, avikesil-s, conception

Introduction
Estrus synchronization is a useful hormonal method for improving reproductive efficiency in small ruminants (Kusina *et al*., 2000) [20] as it allows for timed breeding and lambing, as well as taking advantage of seasonal variations in forage availability, photoperiod, labour resources and market demands. Estrus synchronization in sheep is achieved by shortening or extending the luteal phase of the estrous cycle length using prostaglandin F2α or equivalents, or exogenous natural or synthetic progestagens (Jainudeen *et al*., 2000 and Kusina *et al*., 2000) [13, 20]. Most of the time drugs used in estrus synchronization and ovulation in sheep are steroidal in nature.

Letrozole is a third-generation non-steroidal competitive aromatase inhibitor which binds with heme group of the cytochrome P-450 component of the aromatase enzyme responsible for final and rate-limiting step in the production of estrogens from androstenedione and testosterone (Goss and Strasser, 2001) [8]. Recently, Letrozole drug was demonstrated on cattle for the synchronization of ovulation by prolonging dominant follicle growth and lifespan without affecting progesterone production (Yapura *et al*., 2018) [45]. Letrozole was used for estrus synchronization in sheep (Abdel Dayem *et al*., 2020) [1]. Further, luteotropic effect is an added benefit to increased pregnancy rates, decreased embryo loss in high producing dairy cows (Yapura *et al*., 2018) [45]. Steroid hormones, such as estradiol and progesterone, are perceived to have negative impact on consumer health which led to a ban on the use of steroid hormones in food producing animals in European countries. These concerns have motivated to attempt use letrozole for synchronization of estrus and fertile ovulations in sheep.

Materials and Methods
The present study was carried out on 24 non-pregnant healthy, local cyclic ewes maintained at Livestock Farm Complex, Veterinary College, Hebbal, Bengaluru. The selected ewes were divided into two groups. Ewes in Gorup I (n=12) received letrazole 7.5 mg (Letroprime® 2.5 mg, Leeford, Mumbai) intravaginal sponges and Group II (n=12) received Avikesil-S (350 mg natural progestogen, CSWRI, Avikanagar, Rajasthan, India) intravaginal sponges for 7 days.

On 7th day the sponges were removed in both the groups and intramuscularly injected 125 µg of cloprostenol sodium (Estrumate®, MSD, Mumbai). Letrozole sponges were prepared using polyurethane material 30 mm Length × 20 mm Width × 20 mm thickness and thread of 15 cm length. Sponges were autoclaved and stored in air tight polythene bags. The sponges were loaded with 7.5 mg of Letrozole (3 tablets of Letroprime® 2.5 mg suspended in one mL distilled water w/v) and sponge were dipped and dried before insertion. Permission from the Institutional Animal Ethical Committee was obtained vide No. VCH/IAEC/2021/39 for handling of the animals and carrying out the research.

The ewes were monitored for estrus signs thrice daily for 30 minutes each time using sexually active rams with color marking on their brisket region. The ewes with colour markings on the rump region were considered to be in estrus and have been mated successfully. Ewes were monitored until the diagnosis of pregnancy on day 30th of post mating using Real B mode transrectal ultrasonography. Parameters like sponge retention rate, estrus response rate, estrus duration and conception rate was recorded and analyzed using Fisher's exact chi-square test, then interval to estrus and duration of estrus was recorded and analyzed using two-tailed independent t-test.

Results and Discussion

In the present study, 100% vaginal sponge retention rate (Table 2) was recorded with slight whitish vagina discharge in all ewes of both the groups. Similar retention rates were also observed using FGA sponges for 5 to 7 days by Karaca *et al*. (2009) [14] and Martemucci and D'Alessandro (2011) [25]; and also by using Avikesil-S intravaginal sponge for a period of 7 to 12 days in different breeds of ewes (Mahendra, 2016; Gangadharaiah, 2017; Yadav *et al*., 2020 and Suhas *et al*., 2021) [7, 22, 33, 40]. However, lower sponge retention rate of 94.00% was recorded by Swelum *et al*. (2018) [35] in Najdi ewes using FGA sponge for 14 days. A variety of factors have been reported to influence the vaginal sponge retention rate in the ewes such as as texture and consistency of intravaginal sponge (Martinez-Ros *et al*., 2018) [26], technique of sponge insertion (Romano, 1998), management system (Omontese *et al*., 2012) [27] and size of intravaginal implant (Swelum *et al*., 2018) [35]. Whitish discharge seen in the present study might be due to the physical irritation, inflammatory changes and retention of vaginal secretions caused by the sponges kept *in situ* for long period (Al-Hamedawi *et al*., 2003; Manes *et al*., 2015) [2, 23].

In the present study, 10 out of 12 ewes in both treated groups exhibited estrus signs with the estrus response rate of 83.33% and estrus response rate did not vary between the two treated groups (Table 2). The results were in close agreement with the findings of De *et al*. (2016) [5] (83.85%), Kumar *et al*. (2016) [19] (80.00 and 85.00%) by using Avikesil-S sponges for 12 days with different doses of eCG, Koyuncu and Ozis Altincekic (2016) [17] (81.10%) by using FGA sponges for 7 days combined with PGF2α and PMSG and Lombardo *et al*. (2020)[21] (85.70%) by using MAP sponges for 6 days. On the contrary, lower estrus response rate of 42.85% by Hashema *et al*. (2015) [11] and 66.67% by Sejian *et al*., (2012) [31] were recorded in ewes using different protocols. Interestingly, 90 to 100 per cent estrus response rate was recorded by Swelum *et al*. (2015) [34], Mahendra (2016) [22], Yadav *et al*. (2020) [40] and Suhas *et al*. (2021) [33] using different estrus synchronization protocols. The difference in estrus response rate of present study compared to others studies could be ascribed to the season, PGF2α analogues and breed variations when the study was performed (Gangadharaiah, 2017) [7]. Moreover, in the present study only Avikesil-S sponges with PGF2α was used to synchronize estrus without eCG and probably this might account for the lower estrus response obtained in the current study. Further, Hafez (2000) [10] reported that administration of eCG at sponge removal affects the development of number of follicles which in turn affects estrus response.

The mean interval to estrus in Group I and Group II was 89.4 ± 2.24 h and 45.59 ± 1.57 h, respectively (Table 1). The interval to estrus in Group I was significantly longer (p<0.05) than in Group II. Abdel Dayem *et al*. (2020) [1] recorded interval to estrus of 54.00±0.40 hrs in Farafra ewes using letrozole sponges for 5 days which is shorter than that of the present study using letrozole sponges. Longer interval to estrus recorded in the present study might be due to the higher volume of distribution of the drug as reported in cattle (8 L/kg) by Yapura *et al*. (2014) [44] as compared to women (2 L/kg) (Sioufifi *et al*., 1997) [32] that leads to high tissue accumulation of active drug and relatively slow elimination after sponge removal. Keeping the sponges for 7 days might lead to more tissue accumulation of the active drug and slow elimination that might be responsible for the delay in rise of estradiol which is responsible for the exhibition of estrus signs and preovulatory LH surge (Yapura *et al*., 2015) [41]. The longer time taken for onset of estrus in the present study might also accounts for the longer half-life of letrozole (33 h in cattle) and the preovulatory estradiol concentrations rises 24 h after sponge removal (Yapura *et al*., 2013) [43], hence delayed the onset of estrus.

In the present study, the mean interval to estrus in Group II using Avikasil-S® sponges was 45.59±1.57 hrs, which is almost similar to the interval to estrus of 45.33±1.76 h (Suhas *et al*., 2021) [33] and 42.00±1.81 hrs (Gangadharaiah, 2017) [7] recorded using Avikesil -S sponges. However, lower interval to estrus of 35.00±0.94 hrs by Mahendra (2016) [22], 28.73±1.00 hrs by Yadav *et al*. (2020)[40], 32.00±2.00 hrs by Suhas *et al*. (2021) [33], 33.00±3.75 hrs by Lombardo *et al*. (2020) [21] and 32.9±7.40 hrs by Cavalcanti *et al*. (2012) [4]. The variability in the mean estrus onset duration recorded in present study as compared to the previous reports could be due to the follicular status of the individual ewe and stage of the estrous cycle at which PGF2α was administered (Quirke *et al*., 1979) [29], differences in breed, nutrition, season, use of gonadotrophins and presence of the male after sponge removal (Zeleke *et al*., 2005) [46].

The mean duration of estrus in Group I and Group II was 34.85±1.83 h and 34.7±1.31 h, respectively and the mean duration of estrus among the treated groups was not significant (Table 1). The duration of estrus in Group I was longer than the duration of spontaneous estrus 25.17±0.24 h recorded by Abdel Dayem *et al*. (2020) [1] using Letrozole intra-vaginal sponges. The duration of estrus observed in the present study is similar to the reported estrus duration of 32.10±1.70 h by Ozyurtlu *et al*. (2011) [28], 32.00±2.54 h by Lombardo *et al*. (2020) [21], 32.00 h by Sejian *et al*. (2012) [31], 33.50±0.74 h by Mahendra (2016) [22] and 32.00±2.00 h by Suhas *et al*. (2021) [33] compared to that of Group II of the study. However, shorter estrus duration has been recorded as 27.00±0.80 h by Kulaksiz *et al*. (2013) [18], 27.27±1.40 h by

Khalilavi *et al*. (2016) [16], 28.00±2.00 h and 30.67±2.11 h by Suhas *et al*. (2021)[33], 26.40±1.64 h (Yadav *et al*. 2020) [40], 23.19±1.50 and 23.59±1.28 h (Kumar *et al*. 2016) [19] and 29.00±1.80 h (Gangadharaiah, 2017) [7]. Texeira *et al*. (2016) [36] recorded longer estrus duration of 39.00±14.00 and 42.00±12.80 h. The difference in the estrus duration might also be due to the variation in the dosage of gonadotropin, duration of treatment along with the difference in age and reproductive status of the ewes (Wildeus, 2000) [39]. In the present study PMSG/eCG was not used and this might be the reason for differences in the mean duration of estrus recorded in the present study as compared to the previous studies. Further, differences in breed, nutrition and presence of the male after sponge removal are known to influence the duration of estrus (Greyling *et al*., 1997; Ungerfeld and Rubianes, 1999; Zeleke *et al*., 2005) [9, 37, 46]. The reason for the variation in duration of estrus might be attributed to blood estrogen level and age of ewes (Hashemi *et al*., 2006) [12]. The high levels of serum estrogen concentrations are reported to be responsible for variation in duration of the estrus and also it prolongs the duration of estrus if the concentration is higher (Dogan and Nur, 2006) [6].

The conception rate recorded in the present study in Group I and Group II were 70 and 50 per cent, respectively which were statistically not significant (Table 2). Previous studies have reported improved ovulation rates in estrus synchronized cows with Letrozole (Yapura *et al*. 2011) [42], besides it has luteotropic effect and may improve conception rates (Yapura *et al*. 2018) [45]. The higher conception rates in ewes synchronized with Letrozole in the present study might be attributed to luteotropic effect of Letrozole which culminated relatively higher conception rates obtained in the estrus synchronized ewes.

In Group II ewes, 50 per cent conception rate was recorded which is in close concordance with the conception rate of 55.55 per cent recorded by Suhas *et al*. (2021) [33] in Hassan breed ewes estrus synchronized with Avikesil-S sponges for 7 days with cloprostenol and buserelin acetate 36 hrs after the sponge removal and 57 per cent recorded by Cavalcanti *et al*. (2012) [4] using 60 mg MAP sponges for 6 days combined with eCG and d-cloprostenol 24 h prior to sponge removal. Previous studies in ewes using Avikesil-S sponges for varying periods of 7 to 12 days along with different doses of eCG/ PMSG and PGF2α have reported a conception rates of 83.30% (Sejian *et al*., 2012) [31], 100.00% (Manvi 2014), 66.66% (Mahendra, 2016) [22], 75.00 and 80.00% (Kumar *et al*., 2016) [19], 86.67% (Yadav *et al*., 2020)[40] and 77.77% (Suhas *et al*., 2021) [33].

The higher conception rate in previous studies could be attributed to exogenous gonadotropin (PMSG) administration which resulted in efficient follicles development and ovulation and promoted proper luteinization to form CL (Valentim *et al*., 2016) [38]. Further, it has also been reported that the administration of PMSG is more effective in less prolific and less seasonal breeds of ewes (Omontese *et al*., 2012) [27]. In the present study, since no gonadotropin was used in both the groups, which might be reason for lower conception rates obtained in estrus synchronized ewes with Avikesil-S®. However, much lower conception rates of 16.66% (Mahendra, 2016) [22] and 41.66% (Gangadharaiah, 2017) [7] are also reported using Avikesil-S sponges for varying periods of 11 and 7 days along with different doses of eCG/ PMSG and PGF2α in NARI Suvarna ewes and Bandur ewes, respectively compared to the present study. Variations in conception rate in current study and different studies might be due to difference in population size, the breed (Karagiannidis *et al*., 2001) [15], hormonal protocol used, body condition, effect of ram and breeding season (Ataman *et al*., 2006) [3].

Table 1: Effect of synchronization protocols on parametric reproductive traits in ewes (Mean ± SE)

Sl. No.	Parameters	Letrozole Group I (n=12)	Avikesil-S (Group II) (n=12)
1	Interval to estrus (h)	89.4±2.24a	45.59±1.57b
2	Duration of estrus (h)	34.85±1.83	34.7±1.31

Note: The values bearing superscripts (a, b) vary significantly ($p<0.05$)

Table 2: Effect of synchronization protocols on non-parametric reproductive traits in ewes

Sl. No.	Parameters	Letrozole (Group I, n=12)	Avikesil-S® (Group II, n=12)
1	Sponge retention rate (%)	100.00	100.00
2	Estrus response rate (%)	83.33	83.33
3	Conception rate (%)	70.00	50.00

Conclusion

It was concluded that the locally prepared Letrazole sponges are as effective and suitable as Avikasil-S sponges for estrus synchronization in ewes as they prove 100% sponge retention rate. Letrozole was as effective as natural progesterone in ewes for estrus synchronization in terms of estrus response (83.33%) and conception rate (70%). Hence, the non-steroidal aromatase inhibitor, Letrazole can be considered as one of the alternative to steroidal drugs like progesterone for effective estrus synchronization in ewes. Further, it requires intensive studies in large population to record effectiveness of Letrozole in ewes and also requires *in vivo* pharmaco- kinetic studies on intravaginal Letrazole sponges in ewes.

Conflict of Interest

There is no conflict of interest among the authors.

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