



Modification of O-ring intrauterine devices (IUDs) in mares: Contraception without estrus suppression

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ARTICLE INFO

Keywords:

Intrauterine device
O-ring
Y-design
Contraception
Estrous suppression

ABSTRACT

A significant welfare concern for those within the horse industry is that of the overpopulation in free-roaming horses in the western US. The goal of the present study was to identify a humane and inexpensive means of providing contraception and reducing pregnancy rates in a way that could be applied to free-roaming horses on the western U.S. open range lands. A series of studies was conducted utilizing the previously-described silastic O-ring intrauterine devices (IUDs). Throughout these studies pregnancy was successfully prevented in mares with an O-ring IUD, but collective retention rates failed to exceed 50% regardless of size or durometer (material hardness/malleability). When the O-ring IUDs were compared to the recently-described Y-design IUDs (Holyoak et al., 2021) the Y-design IUDs had a markedly greater rate of retention; therefore, the Y-design IUDs would be most appropriate for potential use in free-roaming horses. Assessment of mare records revealed that the vast majority of mares continued to have ovulations and mating continued to occur while the IUDs were in place. A few mares had multiple small ovarian follicles when the IUD was *in utero*. Findings indicate that utilizing an IUD with the expectation of estrus suppression in mares would fail to be fruitful.

1. Introduction

A significant welfare concern for those within the equine industry is that of the overpopulation in free-roaming horses in the western US. On-range population growth of horses on western rangelands in the US has resulted in approximately 82,000 free-roaming horses in an area where range ecologists have established 27,000 as the desired size (based on ecological sustainability) of the population (Bureau of Land Management BLM, 2019). Overpopulation of lands in the western US leading to overgrazing and forage depletion raises significant animal welfare (Fisher, 1983; Scasta et al., 2018; BLM, 2019) and environmental concerns (Levin et al., 2002; Beaver and Brussard, 2004; Beaver and Herrick, 2006).

A second challenge for the horse industry is that of the “difficult” or “misbehaving” performance of mares when in behavioral estrus. Albeit a less severe problem in comparison to free-roaming horse overpopulation, singularly this problem should be considered a welfare concern for those mares ridden by misinformed and frustrated owners or trainers deeming these mares as simply uncooperative. In cases where mares appear to be refractory to behavior modification efforts, uninformed owners may be persistent in seeking

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<https://doi.org/10.1016/j.anireprosci.2021.106864>

Received 26 June 2021; Received in revised form 21 September 2021; Accepted 22 September 2021

Available online 25 September 2021

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an ovariectomy and insist that veterinarians to perform the surgical procedure before documentation between the undesired behavior and estrus exists. This occurs even though there is evidence that estrous behaviors increase in mares after ovarian removal (Whitesell and McDonnell, 2013). For veterinarians, it can be extremely frustrating in attempting to differentiate a lack of “chemistry” between horse and rider, a deficiency of targeted horse training, or a legitimate change in mare behavioral physiology as there are changes in the mare’s estrous cycle.

In addition to the described welfare concerns, another commonality between the issue of the free-roaming horse overpopulation and “misbehaving” mares in behavioral estrus lies in a proposed treatment with intrauterine devices (IUDs). The IUDs have been investigated for a number of years as a solution to both the overpopulation of horses in western rangelands as well as for “misbehaving” performance mares (Daels and Hughes, 1995; Nie et al., 2003; Killian et al., 2006; Vanderwall, 2015; Diehl de Amorim et al., 2016; Campbell, 2018; Gradil et al., 2019). Inconsistent research results reported in the literature that is easily available to owners continues to emphasize ovariectomy as a potential solution for the “difficult estrus mare” (Campbell, 2018; Melgaard et al., 2020).

The initial focus of this study was to develop a humane and inexpensive means of reducing pregnancy rates within the US free-roaming horse population. Furthermore, during the period this study was being conducted data were collected for which there was subsequently some important points of discussion concerning the effectiveness of an IUD as a method of suppression of behavioral estrus in the mare.

Based on previous results from research where there was insertion of O-ring IUDs into the uteri of six mares with a greater than 80% retention rate (Daels and Hughes, 1995), there was a series of studies conducted in which there was examination of the efficacy and safety of several sizes and hardness increments (i.e., durometer) of an O-ring IUD composed of a silastic elastomer polymer (Baldridge et al., 2017). There was a proof of concept study designed and conducted with the hypothesis being silicone O-ring IUDs would be retained within the uterus and as a result providing an approach for preventing pregnancy in mares in pasture breeding conditions. A desired rate for IUD retention was established as >75%.

2. Materials and methods

2.1. Animals

As many as 24 Quarter Horse mares and two Quarter Horse stallions were utilized for three phases of the present studies that were conducted in 2015 and 2016. The research conducted in 2015 was a pilot study in which there was utilization of only five mares with there being no stallions utilized in the pilot study.

2.2. Ethics approval

Animal use and care procedures were approved by the Oklahoma State University Institutional Animal Care and Use Committee (VM15–29).

Table 1

In utero IUD retention rates during summer of 2016; IUDs were inserted on 18 July 2016; remaining IUDs were removed on 9 September 2016; *IUDs were maintained *in utero* for the complete observation period of 53 days; ($P = 0.09$).

Mare ID	IUD size (mm)	Date IUD expulsion	Days IUD retained	Total number IUDs lost
143	50–75	7/22	4	4/4
130	50–75	7/26	8	
618	50–75	7/28	10	
606	50–75	8/5	18	
612	55–40	7/26	8	4/4
609	55–40	8/2	15	
610	55–40	8/12	25	
616	55–40	8/16	29	
605	55–75	7/19	1	2/4
150	55–75	9/2	46	
601	55–75		*	
603	55–75		*	
123	60–40	7/22	4	1/4
620	60–40		*	
607	60–40		*	
619	60–40		*	
614	60–75	7/22	4	2/4
613	60–75	8/2	15	
611	60–75		*	
615	60–75		*	

2.3. Pilot study design

In the fall of 2015, a pilot study was performed where 50 durometer O-ring IUDs (outside diameter of 40 mm) were placed into the uteri of five mares. Transrectal palpation and ultrasonographic examinations (ibex® EVO® with 5–7 MHz linear transducer, E.I. Medical Imaging®) were performed twice weekly to determine whether the IUD remained *in utero*. After there were unsatisfactory retention rates utilizing the 40 mm, 50 durometer O-ring IUD, the decision was made to increase the durometer scale value for and the diameter of the IUDs in efforts to increase uterine retention rates.

2.4. O-ring IUD mating study design

In the summer of 2016, there continued to be evaluation of the 40 mm diameter IUD but with increased durometers of 55 and 60. Additionally, 75 mm diameter IUDs were also evaluated that had a durometer scale value of 50, 55, and 60. There were 20 mares that were randomly assigned to be administered IUDs of each size (40 or 75 mm) and with a durometer scale value of 50, 55, or 60 that were inserted into four uteri. The 40 mm IUD with a durometer scale value of 50 was not utilized in this portion of the study because it was previously evaluated in the fall of 2015. The 20 mares were then assigned to two groups and mares of each group were placed in a paddock with a breeding stallion that had undergone a standard breeding soundness examination with there being no abnormalities identified at the time of physical examination, reproductive examination, or semen analysis. After administering an IUD, the mares were immediately placed in a paddock with a previously assigned stallion to allow for behavioral estrus and mating to occur while there continued to be transrectal palpation and ultrasonographic examinations performed twice weekly for the ensuing 53-day study duration.

There was determination that the IUDs with a scale value of 60 durometers had a greater rate of *in utero* retention after 53 days (Table 1). It, therefore, was decided to re-evaluate the IUDs with the durometer scale value of 60 durometer in a larger number of mares. Additionally, two batches of IUDs were manufactured with larger durometer scale values of 70 and 80. Because results were similar for both the 40 and 75 mm diameter IUDs, where more than half of the IUDs were not retained *in utero* for a 30 day period, the decision was to produce the IUDs with a 70 and 80 durometer scale value that were 40 mm in diameter and observe for IUD *in utero* retention rates for a period of 28 days. The working hypothesis was that, with the IUDs with a greater durometer scale value, these devices would be less malleable during uterine contractions (potentially an important characteristic for an IUD when there is estrus and during the process of mating) and, therefore, the IUD would be less likely to be expelled. There was utilization of 24 mares by assigning them to three groups with each group having eight mares with different IUDs with a different durometer scale value (60, 70, and 80). The mares were then placed back into a paddock with a breeding stallion.

Table 2

In utero IUD retention rates for 60, 70, and 80 durometer scale values for IUDs; IUDs were inserted on 20 September 2016 and removed 18 October 2016; *IUD was retained *in utero* for the complete observation period of 28 days; ($P = 0.51$).

Mare ID	IUD size (mm)	Date IUD expulsion	Days IUD retained	Total number IUDs lost
602	60–40	9/27	7	5/8
605	60–40	9/27	7	
614	60–40	9/30	10	
620	60–40	10/4	14	
611	60–40	10/18	27	
601	60–40		*	
607	60–40		*	
619	60–40		*	
604	70–40	9/21	1	3/8
609	70–40	9/23	3	
603	70–40	9/27	7	
150	70–40		*	
612	70–40		*	
615	70–40		*	
618	70–40		*	
617	70–40		*	
610	80–40	9/23	3	3/8
123	80–40	9/27	7	
613	80–40	10/11	21	
143	80–40		*	
151	80–40		*	
606	80–40		*	
130	80–40		*	
616	80–40		*	

2.5. Statistical analysis

Analysis of retention rates for IUDs was performed using the Chi square test utilizing Prism analysis software. There were considered to be mean differences when there was a $P = <0.05$ and a tendency for differences when there was a $P \leq 0.10$ and > 0.5 .

3. Results

3.1. Pilot study IUD retention rate

Results when there was evaluation of the O-ring IUDs with 40 mm (outer diameter), 50 durometer scale values indicated 40% (2/5) of mares retained the IUD *in utero* during the 2-month period. Of the mares that did not retain the IUD, there was expulsion of the IUD from two-thirds of the mares within 21 days of insertion.

3.2. Mating experiment IUD retention rates

Retention rates for the 40 and 75 mm diameter O-ring IUDs that had durometer score values of 50, 55, and 60 were similar to each other and only 7 of 20 IUDs were retained during the period when mares were in paddocks with stallions and there was mating occurring (Table 1). There were 12 of 13 IUDs that were not retained *in utero* for the 1-month period subsequent to insertion. When there were greater durometer scale values, there tended to be a difference in uterine retention of IUDs ($P = 0.09$). Three mares that were detected to be pregnant were ascertained to have conceived as a result of mating during the first period of behavioral estrus after the expulsion of the IUD from the uterus.

There was retention of 13 of 24 IUDs with durometer scale values of 60 (repeat trial), 70, or 80 on the durometer scale during the experimental period when there was stallion mating with mares (Table 2) with 10 of the 11 IUDs being expelled within 21 days of insertion. Overall, for the IUDs with greater durometer scale values there was no difference in uterine retention rates ($P = 0.51$). Unfortunately, it appeared that even with the adjustments made to the O-ring IUDs, there continued to be a lack of retention of IUDs at the 75% *in utero* retention rate goal.

Pregnancy was not identified in mares with an IUD *in utero*. There were data from only three mares in regards to pregnancy but it is possible that pregnancy rates after IUD loss were greater. This is due to the fact that embryonic vesicles are not visible using ultrasonographic procedures until about 11 days after ovulation and in performing the present studies early-stage pregnancies may have been disrupted by the insertion of IUDs when mares were assigned to a subsequent study. At no time were any of the mares observed to have evidence of vaginal or vestibular irritation (as may be symptomatically evidenced by frequent bouts of urination or vulvar discharge) after the placement of IUDs while 6 of 24 mares were reported to have echogenic fluid within the uterus that was detected when an ultrasonographic examination was performed, at some point during these studies.

3.3. Comparison of O-ring and Y-design IUD retention rates

Holyoak et al. (2021) reported that IUDs with a 60-durometer scale value that were composed of silastic and were of a Y-shaped design met the contraception criteria established for application in free-roaming horses for population. This was most notable with the desired retention rate being $>75\%$ in the absence of induced uterine pathology. With the 60-durometer scale score, there was a retention of the Y-design IUDs in 15 of 20 mares for a period of 463 days. There was expulsion of five IUDs between days 43 and 294 of the experimental period (Holyoak et al., 2021). Retention rates for the IUDs with a 60, 70, or 80 durometer scale score ($n = 24$) were compared with the Y-design IUDs ($=20$) and the *in utero* retention of the Y-design IUDs was markedly greater during the first 28 days of the experimental period (i.e., period the O-ring IUDs with 60, 70, or 80 durometer scale values were evaluated in the current study; $P = 0.001$).

3.4. Effect of IUD on reproductive cyclicity

Results gleaned from reproductive record data, indicated that the use of IUDs did not result in suppression of behavioral estrus or mating behaviors as evidenced by intermittent mating (which were observed during daily feeding by the ranch manager and by veterinarians at times of group processing for ultrasonographic examinations) and as a result of documented ovulations as evidenced by the detection of corpora lutea (CLs) in mares that were administered an O-ring or Y-design IUD. Exceptions to this include three mares which did not have ovulations during the period the O-ring IUDs were *in situ*. The ovaries of these mares contained populations of follicles ranging from “NSF” (no significant follicles) or “MSF” (multiple significant follicles) during the twice weekly ultrasonographic examinations. It would also appear that one mare (i.e., 615) might have had a CL with a prolonged persistence that was still present on a day where an IUD placement occurred (20 September) and that was maintained until IUD removal (18 October). In this mare, a dominant follicle/ovulation was not detected during the 28 day-period the study was conducted (Table 2).

Unfortunately, due to the original study goal of simply identifying retention rates of IUDs, the original study design did not result in collection of quantifiable data that could be evaluated to closely describe day to day ovarian follicular dynamics during the multiple month period. There, however, was three mares (i.e., 616, 616, and 618) that did not have ovulations during the period of time when the O-ring IUDs were *in utero* and during this period there were populations of follicles ranging from “NSF” (no significant follicles) or “MSF” (multiple significant follicles) when there were the twice weekly ultrasonographic examinations performed. With follicle

populations of this type, there would not be expected to be “suppression of behavioral estrus” because there were only basal concentrations of systemic progesterone resulting from no luteal presence during this time period when there IUDs were *in utero*. This is important because when there is luteal production of progesterone, this hormone is a very potent suppressor of behavioral estrus.

4. Discussion

The original intent of the O-ring IUD studies was to identify a contraceptive device that could be utilized in free-roaming horse herds, and while the results from the O-ring IUD studies did not indicate the minimum desired 75% *in utero* retention rate was met, as a consequence, these results did provide impetus to conduct studies using silastic elastomer Y-design IUDs (Holyoak et al., 2021). At the conclusion of the studies with the O-ring IUDs, it was decided to alter the silastic IUD design to mimic those utilized in women and that are described as ‘fundus-seeking.’ Additionally, there was administration of a single injection of BioRelease LA P₄ 300 (BET Pharm, Lexington, KY, USA) at the time of IUD insertion to circumvent breeding behaviors from occurring in the days immediately subsequent to IUD insertions because this is a time period when there is expulsion of many O-ring IUDs from the uterus of mares. There was a 75% retention rate of the Y-design IUDs, with 100% contraception in females where there was retention of the device *in utero* during a 20.5 month study period (Holyoak et al., 2021). Holyoak et al. (2021) speculated that it would appear that an acceptable and potentially long-lasting IUD contraceptive had been developed in a semi-field environment but the thought was that there needed to be evaluation of this type of IUD in field conditions utilizing free-roaming horses.

It has become obvious based on findings in the present study that the optimal combination of size, shape and durometer scale value must be identified for an efficacious IUD *in utero* retention rate. These characteristics are likely very important because one major factor that is unique is the belled glans of the stallion penis that likely induces a high-pressure occurrence when the stallion penis penetrates the cervix during mating (i.e., stallion penis emits an ejaculate through a soft, dilated cervix directly into the uterus).

There has been an enhanced interest in the topic of behavior modification in mares after administration of IUDs subsequent to when there was the initial publication of results gleaned from the data reported in the present study. This renewed interest provided an impetus for further retrospective inspection of individual mare records collected during the evaluation of both the O-ring and the Y-design IUDs. The study design did not allow for collection of quantifiable data that would precisely describe daily changes in follicular dynamics during the multiple month period during which data were collected. There were rather reproductive ultrasonographic examinations conducted twice weekly (for less than 2 months) or bi-weekly for 20 months depending on whether there was O-ring or Y-design evaluations occurring. Even with these schedules, it could be gleaned from the records for the mares included in both the O-ring and Y-design studies that the use of IUDs did not result in suppression of estrus or breeding behaviors as evidenced by observed intermittent mating occurrences, documented ovulations, and development of CL in mares that had an IUD *in utero*. There have been similar results reported in mares with marbles and other intrauterine devices (Daels and Hughes, 1995; Nie et al., 2003; Argo and Turnbull, 2010). From these results, it was ascertained that behavioral estrus suppression should not be expected to occur following insertion of an IUD in either a free-roaming mare or a domesticated performance mare.

Ovarian follicular dynamics in mares where the Y-design IUD was evaluated were more difficult to describe due to the bi-weekly examination interval conducted during much of the study period (Holyoak et al., 2021). It was suspected that few mares had a deviation from normal patterns of ovarian follicular dynamics after IUD insertions into the uterus but this evaluation was even further complicated by individual mare variation with the initiation (or cessation) of the estrous cycle transition phases before and after seasonally-induced anestrus. It is also suspected that variations in mare estrous cyclicity could have occurred as a result of induced endometritis following placement of the IUD (and retention) but, as previously described, the frequency of the bi-weekly ultrasonographic examinations did not lend to detailed documentation of follicular dynamics. In the Holyoak et al. (2021) study, it was documented that in one mare there was development of three CLs (evidenced by the CL development in alternate ovaries) in less than a 30-day period. This mare also had a large amount of uterine fluid present, indicating that an inflammation induced short-estrous cycling effect may have contributed to development of these multiple CL during the study period. It's possible that a second mare could have had a persistent CL on the right ovary for several months because a CL was documented on the right ovary during four consecutive examinations before a CL developed on the left ovary. Because this mare also had a large amount of uterine fluid, however, it cannot be ascertained if this mare continued to have ovulations from the same ovary during this time period or if this mare had retention of a CL that resulted from a spontaneous ovulation with there being a prolonged luteal function as compared to that which typically occurs in mares.

The number of mares in a group that will have spontaneous prolongation of a CL functions has been reported to be 8% in untreated control mares (Nie et al., 2003). Similar to indications in previous studies (Nie et al., 2003; Klein, 2016), it was interesting that in the present study mares having apparent deviations from normal ovarian cyclic patterns were the youngest mares. It was deduced that the vast majority of mares continued to have ovulations throughout the duration of the studies with the O-ring and Y-designed IUDs as evidenced by the presence of CL in ovaries on alternating sides of the reproductive tract. Those mares described (previously in this manuscript) as having these patterns of deviation from normal estrous cyclicity also had basal endogenous progesterone, resulting in an enhanced occurrence of estrus-like behavior, similar to a mare during the winter anestrus period.

Successful suppression of behavioral estrus in mares is problematic because of owner-requested outcomes for equine veterinarians. The owner expectations are to address inhibition of a vast array of mare behaviors such as poor athletic performance, kicking, biting, aggression, excessive urination, vocalizing, tail twitching, etc. (Hooper et al., 1993; Nie et al., 2003; Hedberg et al., 2007; Argo and Turnbull, 2010; Gradil et al., 2019; Melgaard et al., 2020). It may be true that, similar to women athletes, mares can experience a change in neuromuscular performance as a result of ligamentous laxity resulting from changes in reproductive hormone concentrations throughout an estrous cycle (Hewett, 2000). Additionally, actual ovarian pain manifested in the region of the epaxial muscles

during the peri-ovulation period, termed “mittelschmerz” in women, should be considered as a potential reason for lameness or lack of performance in “misbehaving” mares expressing behavioral estrus. “Problem” mares should be examined by a veterinarian at the time at which the owner perceives the behavior to be occurring and examination procedures need to include, not only evaluation of the reproductive tract, but must also include a complete lameness evaluation to identify issues that may or may not be estrogen related.

Confusion between contraception and suppression of behavioral estrus in mares, especially by laypeople, may exist in part due to the public’s experience with the spayed bitch and the dogma that “ovarian removal results in removal of natural breeding behavior” (Pets WebMD <https://pets.webmd.com/reasons-spay-neuter-pet#2-6>). In contrast to the bitch, however, mares that have been ovariectomized express “paradoxical” behavioral estrus and there is often an increase in the frequency of behaviors associated with estrus when compared to ovary-intact mares in which there are cyclical phases of diestrus (Ginther, 1974; Asa et al., 1980; Hooper et al., 1993; Crowell-Davis, 2007). While the concept of utilizing IUDs, as a method of estrous suppression or contraception is not new, there is considerable skepticism due to inconsistent results and induction of uterine pathologies [i.e., shattering intrauterine marbles (Klabnik-Bradford et al., 2013; Turner et al., 2015; Vanderwall, 2015; Diel de Amorim et al., 2016)]. It should be taken seriously that placement of any form of IUD into the uterus of a valuable mare can result in acute endometritis as evidenced by uterine fluid accumulation and edema at the site of the IUD in both the present study and as reported previously (Rivera Del Alamo et al., 2008; Joone et al., 2021). It, however, is equally important to note that there were no adverse effects on the health or welfare of the mares following *in utero* insertions of any of the silastic IUDs during the present study.

Lending to further confusion in the differences between suppression of behavioral estrus and contraception in mares, is the availability of summaries of results or literature reviews that include information on both topics within the same report (Hornberger et al., 2017). On a more specific note, publications or legislative efforts focused on identification of methods for population control in the western US (e.g., GnRH vaccination, PZP vaccination, ovariectomy) describe methods of contraception that may also inadvertently induce behavioral estrus in mares (Garza et al., 1986; Dalin et al., 2002; Killian et al., 2006). Unfortunately, implementation of such methods also lead to the risk of inducing increased frequencies of mating on a long-term basis, reduced mare band-fidelity to the stallion, and lengthening of breeding seasons in free-roaming mares (Powell, 1999; Ransom et al., 2010; Nuñez et al., 2017). Such an increase in behavioral estrus could have an effect on mare and stallion welfare and herd dynamics.

It is recognized that there are two limitations in the present IUD-oriented studies. These include the inability to quantify the number of stallion mounts of each mare and documentation of more accurate inter-ovulation intervals that would have led to a more precise description of estrous cyclicity deviations. Documentation of accurate inter-ovulation intervals would require either ultrasonographic examinations more frequently than every 2 weeks or even weekly serum progesterone analysis; both of which were outside the scope of this project in which the main goal was investigation of IUDs for contraception purposes. It can be presumed the number of mating occurrences during a period of months in mares with an IUD *in utero* is greater than what would occur in a non-treated fertile, free-roaming mares during the same time period due to eventual conception and pregnancy in mares without an IUD. Excessive mating of mares is a concern when mares are not pregnant for a prolonged period of time; however, because the mares in the present study had documented luteal phases (as indicated by the presence of CLs) excessive mating during a 3-week period was not a concern in the present study.

5. Conclusion

While the O-ring IUDs failed to meet the retention rate goal, the subsequently manufactured Y-design IUDs resulted in adequate *in utero* retention and contraception in semi-field conditions (Holyoak et al., 2021). The results from these sequentially-performed studies involving both O-ring and Y-design IUDs indicated the ideal IUD size, shape and malleability must be identified to obtain an acceptable IUD *in utero* retention rates. Continued ovulations were documented in the vast majority of mares in which there was *in utero* retention of O-ring and Y-design IUDs during the experimental period.

Veterinarians have an ethical responsibility for educating owners of the conflicting evidence that exists in regard to IUDs resulting in enhanced mare performance as a result of suppression of behavioral estrus. Other significant reasons for subpar mare performance should not be overlooked and full lameness and reproductive examinations should be performed in combination before resorting to invasive procedures (e.g., ovariectomy) or methods that lack evidence-based information (e.g., IUDs) in the performance mare.

Funding

This research was supported by the Bureau of Land Management [grant no. G16AC00050].

CRedit authorship contribution statement

CCL, SSG, AJK, GRH participated in the conceptualization of the study, analysis of data, and approval of the manuscript. CCL, JMB, COA, and GRH participated in data collection.

Declarations of Competing Interest

The authors report no declarations of interest.

Acknowledgements

Colleagues, students, and former veterinary residents contributed greatly to this study and provided much needed support. This work would have not been possible without the dedicated service, herd and pasture management from our ranch manager, Dennis Wilbourn, RVT.

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