IMPACT OF FESCUE TOXICOSIS ON THE SUCCESS OF REPRODUCTIVE TECHNOLOGIES

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Introduction

Tall fescue (*Lolium arundinaceum* [Schreb.] Darbysh.), primarily Kentucky (KY)-31, is a cool-season perennial forage heavily utilized by cow-calf producers in the Southeast to Midwest U.S. regions (Ball et al., 2007). Kentucky (KY)-31 tall fescue has a symbiotic relationship with a fungal endophyte (*Epichloë coenophiala*) that produces ergot alkaloid toxins. Fescue toxicosis is a result of cattle grazing endophyte-infected tall fescue, specifically consuming ergot alkaloid toxins produced by the endophytic fungus. It is estimated that 90% of KY-31 pastures, which encompass approximately 35 million acres in the U.S., commonly called the "fescue belt", are infected with the *Epichloë* endophyte (Burns and Chamblee, 1979; Strickland et al., 2009). Consumption of endophyte-infected tall fescue negatively impacts intake, weight gain, circulating prolactin concentrations, reproductive performance, milk production, and causes increased body temperatures (reviewed by Strickland et al., 2011) and it is speculated that fescue toxicosis contributes to over $2 billion in annual economic loss to the U.S. livestock industries (reviewed by Kallenbach, 2015).

Considerable progress has been made in determining the timing of reproductive loss associated with fescue toxicosis (Porter and Thompson, 1992; Poole and Poole, 2019). Collectively, reproductive failure in cattle following ergot alkaloid exposure can be attributed to changes in sperm motility and morphology, altered ovarian follicle development, ovarian dysfunction, and reduced circulating steroid hormone concentrations, subsequently leading to reduced pregnancy rates (reviewed by Porter and Thompson, 1992). However, the complex nature of this syndrome makes defining the exact reason for reproductive failure difficult and there are inconsistencies in the literature when examining fescue toxicosis impact on reproductive performance. Table 1 summarizes pregnancy, conception or calving rates that have been reported for cattle exposed to endophyte-infected tall fescue compared to other non-toxic forages. This high variability in animal response could be due seasonal or annual fluctuations in toxin load in combination with the age and genetic background of the animal, and/or elevated environmental temperature which would influence reproductive tract function and has hindered our ability to alleviate the symptoms of fescue toxicosis. There are limited studies that specifically examine that impact of fescue toxicosis on reproductive techniques, thus the focus of this article will explore how exposure to ergot alkaloid toxins could impact reproductive success following use of the reproductive technologies and potential strategies to mitigate the negative effects on reproductive performance.

Does fescue toxicosis affect estrous synchronization programs?

Estrous or ovulation synchronization in beef cattle involves manipulating the females' estrous cycle, through hormone supplementation, to reset the follicular waves on the ovary so they will ovulate and can be bred at about the same time. Precise coordination and communication between the various reproductive organs is critical to ensure success of these synchronization programs. Reproductive organs, like the ovary, uterus and pituitary, release hormones into the

bloodstream, which carries them to other reproductive tissues to stimulate the desired response to regulate the reproductive processes. Numerous studies have demonstrated that reduced blood flow to the reproductive organs negatively impact ovarian function and reduces fetal development and growth (reviewed by Meschia, 2011). Ergot alkaloid toxins, produced in endophyte-infected tall fescue, have vasoconstrictive actions on the blood vessels and a couple of studies have used Doppler ultrasonography to show that heifers chronically exposed to endophyte-infected tall fescue have reduced caudal artery area and blood flow to the peripheral arteries when compared to heifers consuming endophyte-free tall fescue (Aiken et al., 2007; Poole et al., 2018), however literature describing the extent to which vasoconstriction occurs to the internal organs is limited (Klotz, 2015).

Recently, Poole et al. (2018) investigated if chronic exposure of ergot alkaloids, via ground KY31 fescue seed, would decrease the diameter of the utero-ovarian blood vessels thus reducing systemic blood flow to the ovary during various stages of the estrous cycle. Ovarian artery and vein area was measured via Doppler ultrasonography on days 0, 4, 10, and 17 to represent both the follicular and luteal phases of the estrous cycle. Ovarian artery area was not different on days 0 and 4 of the estrous cycle, however ovarian artery area was reduced on days 10 and 17 in heifers consuming ergot alkaloids compared to heifers fed the non-toxic diet (Figure 1). Additionally, minimal changes were observed in the ovarian vein area, most likely due to the reduction of vascular smooth muscle cells surrounding veins compared to arteries (Figure 1). These data demonstrate that the symptoms of fescue toxicosis reduced the ovarian artery area which restricts blood flow and limits hormone signals and nutrient to the ovary potentially leading to reduced responsiveness of hormonal supplementation during estrous synchronization programs and reduced reproductive performance.

Table 1: Summary of pregnancy, conception or calving rates that have been reported for cattle exposed to endophyte-infected tall fescue compared to other non-toxic diets.

Pregnancy Rates				
Location	***Non-toxic Diet***	***Toxic (E+) Diet***	***Change***	***Reference***
Alabama	96	55	Decrease	Schmidt et al., 1986
Kentucky	95	55	Decrease	Gay et. al., 1988
Tennessee	85	60	Decrease	McKenzie et. al., 1991
Alabama	73	57	No Difference	Rahe et. al., 1991
Alabama	72	31	Decrease	Rahe et. al., 1991
North Carolina	68	47	Decrease	Washburn and Green, 1991
Illinois	35	21	No Difference	Mahmood et.al., 1994
Tennessee	32	50	No Difference	Barnett et. al., 1998
North Carolina	47	31	Decrease	Poole et. al., 2019
Conception Rates				

Location	*Non-toxic Diet*	*Toxic (E+) Diet*	*Change*	*Reference*
Tennessee	100	54	Decrease	Ashley et. al., 1987
North Carolina	74	78	No Difference	Washburn et. al., 1989
Arkansas	74	78	No Difference	Rorie et. al., 1998
Calving Rates				
Location	*Non-toxic Diet*	*Toxic (E+) Diet*	*Change*	*Reference*
Arkansas	90	80	No Difference	Beers and Piper, 1987
Arkansas	82	78	No Difference	Brown et.al., 1992
Arkansas	92	79	Decrease	Brown et.al., 1997
Arkansas	93	56	Decrease	Brown et.al., 2000

With the potential for reduced blood flow to the ovary restricting essential nutrients for normal ovarian function, several has investigated the impact of fescue toxicosis of follicular development. McKenzie and Erickson (1989; 1991) observed a decrease in the diameter and number of large follicles in heifers consuming endophyte-infected tall fescue. Likewise, Burke and Rorie (2002) examined follicular development and estrogen concentrations in lactating beef cows grazing endophyte-free (EF) or endophyte-infected (EI) tall fescue. No difference were found in the number of class 1 (small; 3 to 5 mm) and class 3 (large; >10 mm) antral follicles between treatments. Conversely, the number of class 2 (medium; 6-9 mm) follicles were reduced in cows grazing EI fescue compared to cows grazing EF fescue. Similarly, Poole et al. (2018) observed that 6 to 9 mm follicle number was reduced in heifers consuming ergot alkaloids. The 6 to 9 mm follicle size can be classified as selected follicles, and are of critical importance to follicular development with the gonadotropin dependence switching from FSH to LH. These results suggest that exposure to ergot alkaloids may hinder follicular selection though inadequate delivery of gonadotropins and other nutrients due to insufficient blood flow to the ovary.

Additionally, many of the symptoms of fescue toxicosis in cattle are amplified during periods of heat stress when the animal lacks the inability to maintain a thermoneutral body temperature due to increased ambient temperatures. Heifers consuming the EI seed in heat stress conditions resulted in a decreased number of large follicles (> 9 mm) in addition to having a smaller preovulatory follicle diameter compared to control heifers (Burke et al., 2001).

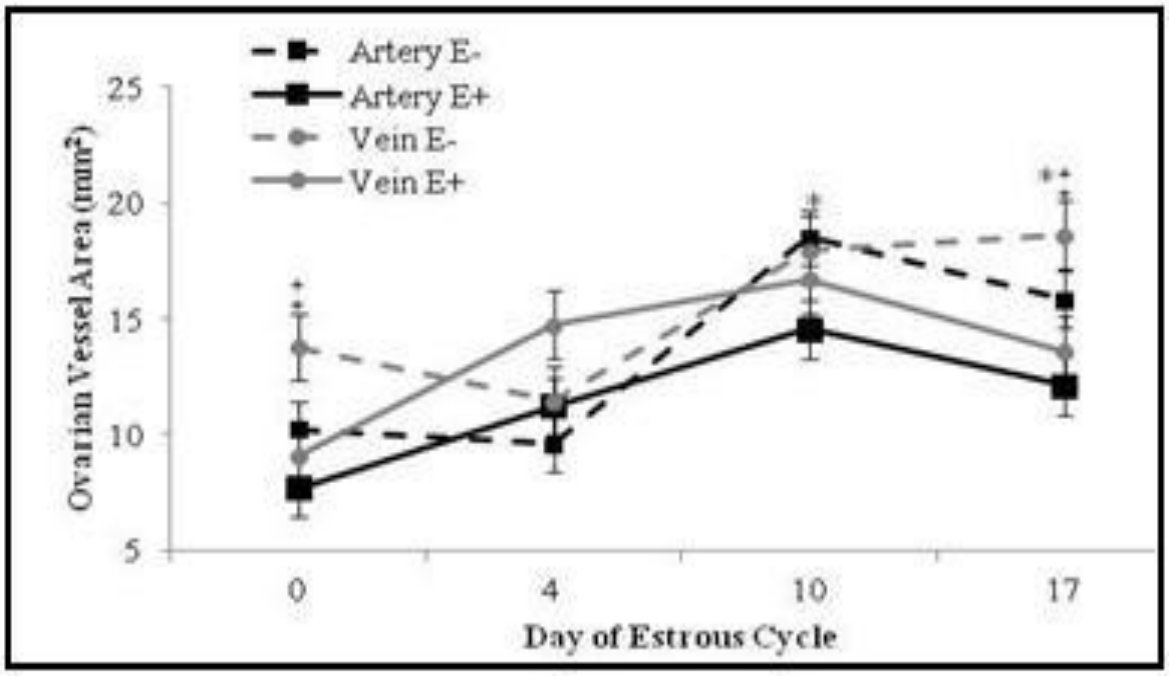

Figure 1. Changes in ovarian artery (black lines) and vein (gray lines) area (mm2) in beef heifers chronically exposed to either EI or EF fescue seed. *Effect of treatment ($P < 0.01$); treatment × d interaction ($P < 0.05$) for ovarian artery. ‡Effect of treatment ($P < 0.01$); treatment × d interaction ($P < 0.01$) for ovarian vein (adapted from Poole et. al., 2018).

Recently, a genetic trait has been identified in *Bos taurus*-influenced breeds, Senepol and other Criollo cattle breeds, which is associated with high heat tolerance and a slick hair coat (Olsen et al., 2003). Therefore, Poole et al. (2019) evaluated the effect of the slick trait and exposure to ergot alkaloids on follicular dynamics in heat stressed beef heifers. Heifers consuming the EI fescue with a wild-type hair coat (lacking the slick hair mutation) had an increase in the number of preselected follicles (2 to 4 mm; Figure 2A), however, no change in the number of selected follicles (5 to 8 mm), yet a decrease in the number of preovulatory follicles (>9 mm; Figure 2B) compared to the other heifer groups (wild-type hair coat consuming EF fescue and heifers with a slick-type hair coat consuming EI or EF fescue). Intriguingly, this lack of follicular transition indicates a dysregulation during follicular selection during folliculogenesis that was not observed in heifers possessing the slick hair trait and consuming the EI fescue. Taken together, the changes in follicle dynamics due to exposure to ergot alkaloid toxins found in endophyte infected tall fescue under both thermoneutral and heat stress conditions could result in females failing to response to the hormone supplementation involved in estrous synchronization protocols.

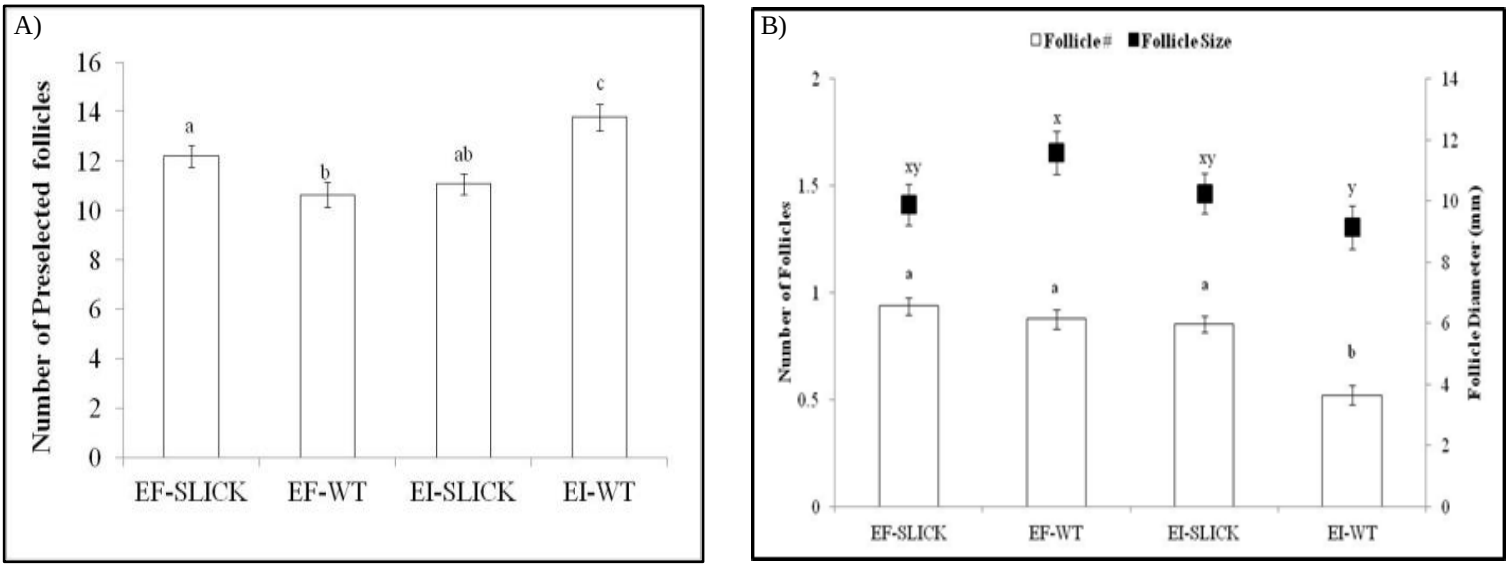

Figure 2. (A) Increased number of preselected (2-4 mm) follicles in heifers with wildtype hair coat exposed to ergot alkaloids (EI-WT) compared to heifers with the slick hair trait consuming ergot alkaloids (EI-SLICK), as well as the control heifers (no ergot alkaloids) with slick (EF-SLICK) or wildtype hair coat (EF-WT); (B) Decreased in the number (white bars), and smaller average size (black boxes), of selected (>9 mm) follicles in heifers with wildtype hair exposed to ergot alkaloids (EI-WT) compared to heifers with the slick hair consuming ergot alkaloids (EI-SLICK), as well as the control heifers (no ergot alkaloids) with slick (EF-SLICK) or wildtype hair (EF-WT; adapted from Poole et. al., 2019).

Does fescue toxicosis impact artificial insemination success?

Since the precise mechanisms of how or at what stage of the reproductive cycle ergot alkaloids in endophyte infected tall fescue alters the reproductive tract remains unknown, it is possible these changes are negatively impacting artificial insemination (AI) pregnancy rates and response to estrous synchronization. Several studies have examined first service conception rates to AI following exposure to endophyte infected tall fescue. A study conducted in Alabama, reported that 96% of beef heifers raised on low-endophyte fescue conceived, compared with 55% of those raised on high-endophyte fescue (Schmidt et al., 1986). Washburn and colleagues (1989) tracked artificial insemination (AI) conception rates in replacement beef heifers exposed to high and low levels of endophyte-infected fescue pastures over a 3 year period. Conception rates in the replacement beef heifers exposed to high-endophyte fescue were 11% compared to 58% in heifers exposed to low-endophyte fescue in the first-year, 63% versus 84% in the second year, and 42% versus 53% in the third year. While conception rates for the high-endophyte–exposed heifers were reduced for the first 2 years of the study; overall conception rates in these replacement beef heifers over the 3-year period were 74% and 78% for the high- and low-endophyte groups, respectively. In a follow up study, these authors confirmed the negative impact of fescue toxicosis of AI conception rate with 47% of animals on high-endophyte fescue conceived via AI, versus 64% of those on low-endophyte fescue pasture (Washburn and Green, 1991; Table 1), confirming the negative impact of fescue toxicosis on AI success. More recent studies have examine the impact of grazing EI fescue pre or post insemination. Burn (2012) demonstrated the 2- and 3-yr old beef

cattle grazing EI fescue pastures prior to AI resulted in decreased cumulative pregnancy rates at day 30 (41.9% vs. 62.8%), 60 (55.0% vs. 77.0%), and 130 (69.1% vs. 87.4%), compared to cattle grazing non-toxic forages prior to AI. Additionally, switching cattle to EI fescue pastures following AI decreased cumulative pregnancy rates at day 60 (55.0% vs. 76.9%), and 130 (66.8% vs. 89.8%), but not day 30 (50.7% vs. 54.1%), compared to cattle grazing non-toxic forages (Burns, 2012). Ultimately, grazing EI pastures prior to or switched to EI pastures following AI resulted in decreased pregnancy rates compared to cattle grazing non-toxic pastures, however it remains unclear whether the pregnancy loss occurs due to poor oocyte quality, reduced fertilization rates, or hindered early embryonic development.

Early studies demonstrated fescue toxicosis had limited impact on a bulls breeding potential based on the classic breeding soundness exam (BSE) consisting of scrotal circumference measurement, a physical exam of the bull, and assessment of semen quality (motility and morphology). Initial studies showed no differences in sperm motility or morphology immediately after collection and in fresh extended semen between bulls exposed to either EI or EF fescue pastures (Schuenemann et al., 2005a, b) or EI tall fescue seed (Jones et al., 2004). However, Looper et al. (2009) grazed bulls on either the ergot alkaloid–producing KY31 or a novel nontoxic endophyte for 121 d and observed a 20% reduction in sperm motility and progressive motility during the months of July and August; however, the means reported still showed acceptable levels of motility required for passing a bull breeding soundness exam. In a recent study, a 20% decrease in normal sperm cell morphology was observed when bulls grazed EI (KY31) pastures in contrast with bulls that grazed EF fescue during the summer months of July and August (Pratt et al., 2015). In contrast, there were no reports of any negative effect on semen quality when bulls received high-energy rations containing defined concentrations of ergot alkaloids, thus these effects on semen quality may be related energy intake as opposed to exposure to toxins (reviewed by Pratt and Andrae, 2015).

Others have examined the impact of fescue toxicosis on cryopreservation of sperm cells for AI, and discovered that extended semen from bulls exposed to EI fescue resulted in a reduction of viable spermatozoa post-thaw (Gallagher and Senger, 1989). Specifically, semen frozen from bulls grazing novel, nontoxic endophyte fescue exhibited a 3- to 4-fold greater motility post-thaw after standard freezing procedures when compared with semen from bulls grazing EI fescue, indicating that sperm physiology may be altered due to consumption of EI fescue (Pratt et al., 2015). Embryos generated, via *in vitro* fertilization, using semen from bulls grazing EI fescue resulted in an 18% decrease in embryo formation compared to semen from bulls grazing non-toxic pastures (Schuenemann et al., 2005a, b). Follow up studies have demonstrated that the negative effects of fescue toxicosis on semen quality persist for months past the period which bulls were exposed to the EI fescue (Burnett et. al., 2017). Thus consumption of EI tall fescue decreased sperm motility immediately post-thaw and reduces the sperm cells ability to withstand damages due to cryopreservation. While decreased sperm motility post thaw will hinder reproductive success to AI, this may not be an immediate concern to beef producers since most seedstock operations and genetics companies are located outside the "fescue-belt" of the U.S.A.

Impact of fescue toxicosis on embryo competency and transfer success

A few studies have evaluated the impact that ergot alkaloids in EI fescue have on oocyte competency and early embryonic development. Jones et al. (2009) cultured cumulus-oocyte-complexes with plasma from heifers which grazed EF or EI pastures for 24 d, and found no difference in early embryo development (transition to metaphase II, MII). Additionally, ovum

pick-up was performed on the heifers and the high quality (grade I) oocytes were subjected to plasma from EF or EI heifers during the IVF procedure. Interestingly, there was a difference observed with 66% of the EF grade I oocytes developed to MII stage versus 0% of the EI grade I oocytes, thus demonstrating that in vivo exposure to endophyte-infected tall fescue can directly inhibit proper oocyte maturation (Jones et al., 2009). Schuenemann et al. (2005c) explored the impact of ergot alkaloids on early embryonic development (experiment 1) and uterine receptivity (experiment 2) in vivo. Cattle were allotted to receive either the control (CON) or an ergot alkaloid seed (EI) diet. In experiment 1, uterine horn ipsilateral to the CL was flushed for embryo recovery following estrous synchronization and artificial insemination. Embry recovery tended to be more successful in CON cattle versus EI cattle. Of the embryos recovered, a greater percent of embryos from CON animals had developed to compacted morula or blastocyst, and there was a greater percent of better quality embryos from CON cattle versus ET cattle (Figure 3; Schuenemann et al., 2005c).

In experiment 2, two frozen-thawed good quality embryos were transferred to recipients in both treatment groups seven days following synchronized estrus. Interestingly, pregnancy rates following transfer did not differ (Schuenemann et al., 2005c). The authors concluded that the uterine environment is suitable to maintain pregnancy after day 7 (following embryo transfer) of gestation, however ergot alkaloid exposure appears to detrimentally affect either the oocyte or the early embryo prior to the blastocyst stage.

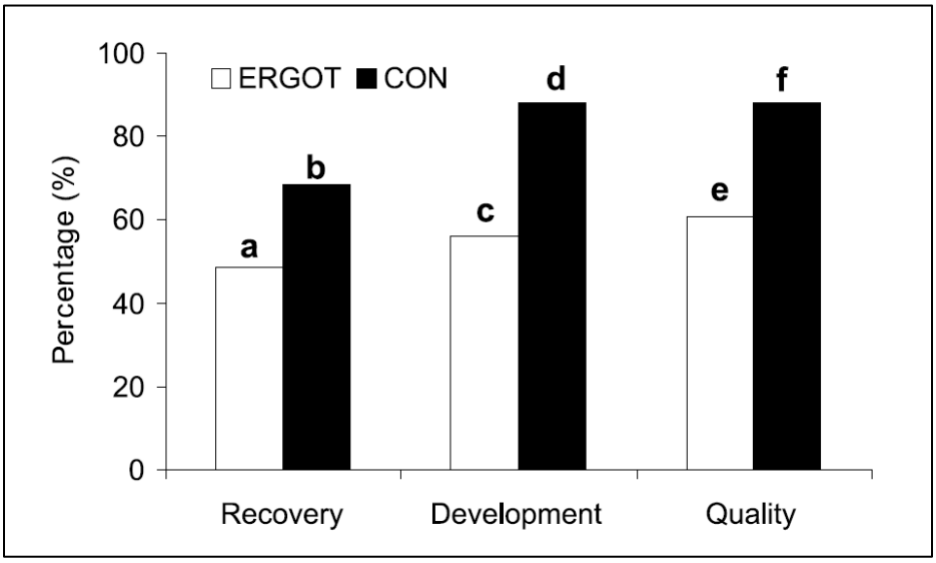

Figure 3: Percentage of embryos that were collected (recovery) by flushing the uterus for a single embryo on day 7 after breeding, had developed to the morula stage (development) and were considered transferable quality (quality) from cows exposed to ergotamine tartrate (ERGOT) compared to control cows (CON). Different letters above bars within embryo stage indicate level of significance or tendency observed (a,b p-0.08; c,d $p<0.05$; e,f $p=0.09$; Schuenemann et al., 2005c)

Conclusions and Potential Solutions:

While evidence of reduced reproductive performance of cattle consuming endophyte-infected tall fescue has been extensively studied in an attempt to find remedies for, or offset the negative impact of fescue toxicosis. Currently, producers have several available options to limit but not completely eliminate the negative effects of fescue toxicosis. Endophyte infected fescue pastures can be either renovated or intensively managed to improve animal performance. Original approaches included inter-seeding legumes into EI fescue pasture (Beck et al., 2008), and /or suppress fescue seedhead production via clipping or chemical control (Aiken and Strickland, 2013). Ongoing studies are exploring effective methods to renovate endophyte-infected fescue pasture where an application of herbicide is followed by a smother crop and then planting of non-toxic fescue (Ingram, 2019). Additionally, supplemental crude protein has been shown to improve growth performance in cattle grazing endophyte-infected tall fescue (Elizalde et al., 1998). Several mineral supplements have been marketed as alleviating the clinical signs of fescue toxicosis, however, there is little scientific evidence available to support their efficacy. Others have presented data that slow-release formulations of thiabendazole and ivermectin prevents some of the adverse effects of the endophyte toxins through limiting the vasoconstrictive activity of ergot alkaloids in EI fescue (Bransby et al., 1993), however there is limited data demonstrating the effectiveness of these products in improving reproductive performance (Volk et. al., 2019). Lastly, producers can alter the timing in which cattle are exposed to the highest concentration of toxins in EI fescue. Producers in the fescue belt can transition their herd from a spring calving and early summer breeding (when toxin concentrations are greatest) system to a fall calving and winter breeding system (when toxin concentrations are decreased). Ultimately, the complex etiology of this syndrome has hindered the exploration of specific mechanisms of action of ergovaline on specific tissues. Seasonal or annual fluctuations in ergot alkaloid concentrations in combination with the age and genetic background of the animal, and/or environmental conditions influence the impact ergot alkaloids have on the reproductive tissues leading to inconsistencies in research. Further exploration into the precise mechanism of action of ergot alkaloids on the reproductive organs through innovative research combining cellular and molecular techniques with applied experimental models will lead to a better understanding of the negative impact these toxins on reproductive processes. Moreover, this knowledge will lead to inventive tools and strategies to enhance best management practices for improved reproductive performance in animals consuming endophyte-infected tall fescue.

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