Exposure to ergot alkaloids during gestation reduces fetal growth in sheep

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INTRODUCTION
Tall fescue [Lolium arundinaceum (Schreb.) Darbysh; Schedonorus phoenix (Scop.) Holub] is the primary cool season perennial grass in the eastern U.S. Most tall fescue contains an endophyte (Neotyphodium coenophialum), which produces ergot alkaloids that cause vasoconstriction and could restrict blood flow to the fetus in pregnant animals. The objective of this study was to examine fetal growth during maternal exposure to ergot alkaloids during gestation. Pregnant ewes (n = 16) were randomly assigned to one of two dietary treatments: (1) endophyte-infected (N. coenophialum) tall fescue seed (E+; 0.8 μg of ergovaline/g diet DM) and (2) endophyte-free tall fescue seed (E−; 0.0 μg of ergovaline/g diet DM). Birth weight of lambs was reduced by 37% for E+ compared to E−. Organ and muscle weights were also lighter for E+ than E−. Exposure to ergot alkaloids in utero reduces fetal growth and muscle development.

Keywords: sheep, ergot alkaloids, fetal growth, muscle development

MATERIALS AND METHODS
All animal experimental procedures were reviewed and approved by the Clemson University Institutional Animal Care and Use Committee (AUP-2011-053).

Southdown ewes (n = 20; BW = 70 kg; BCS = 4) were mated to a single ram that was fitted with a marking harness. Ewes were checked twice daily and crayon marks from the ram’s harness were denoted to estimate breeding date. Ewes were confirmed pregnant via transrectal ultrasonography on d 35 of gestation. Ewes confirmed pregnant (n = 16) were randomly assigned to one of two dietary treatments: (1) endophyte-infected (N. coenophialum) tall fescue seed (E+; 0.8 μg of ergovaline + ergovalinine/g diet DM) and (2) endophyte-free tall fescue seed (E−; 0.0 μg of ergovaline + ergovalinine/g diet DM). Endophyte-infected and endophyte-free tall fescue seed (E+ cv. Defiance, and E− cv. Fawn, turf-type tall fescue seed, Seed Research of Oregon, Tangent, OR) was first analyzed for ergovaline and ergovalinine levels according to Aiken et al. (2009) and then diets formulated to provide the targeted levels of ergovaline/ergovalinine in the diet. Fescue seed was delivered daily in a total mixed ration (Table 1) formulated to meet NRC requirements for pregnant ewes from d 35 to parturition.

Blood samples were collected from the ewes via jugular venipuncture into tubes on d 30, 50, and 130 of gestation. Samples were allowed to clot for 30 min at room temperature and then at 4°C overnight. Serum was obtained by centrifuging at 1000 × g for 15 min at 4°C and stored frozen at −20°C. Prolactin (PRL) concentrations were measured using RIA according to the procedures of Bernard et al. (1993).
Table 1 | Composition of the total mixed ration containing endophyte-infected tall fescue seed fed to the ewes during gestation.

| Ingredient                  | % of ration, DM |
|-----------------------------|-----------------|
| Tall fescue seed            | 38.5            |
| Cottonseed hulls            | 15.4            |
| Molasses                    | 8.6             |
| Corn grain, cracked         | 18.9            |
| Soybean hulls               | 11.4            |
| Limestone                   | 0.2             |
| Soybean meal                | 2.8             |

**NUTRIENT COMPOSITION, DM BASIS**

| Ingredient | % of ration |
|------------|-------------|
| Crude protein | 11 %       |
| TDN         | 60%         |

At parturition, a male lamb (E+ = 8; E− = 8) was removed from each ewe carrying twins. If two male lambs were born to the same ewe, the firstborn male lamb was removed from the dam. Male lambs were given a fixed amount of artificial colostrum (Lamb’s Choice Total, The Saskatoon Colostrum Co., 3 oz. reconstituted dried bovine colostrum) and harvested within 12 h of birth. The attending veterinarian euthanized lambs with an overdose of pentobarbital. Live weight was collected for each lamb and then the lamb was exsanguinated. The hide, head, feet, and tail were removed and weight of the carcass obtained. Weights and then the lamb was exsanguinated. The hide, head, feet, and tail were removed and weight of the carcass obtained. Weights were collected on all organs and total digestive tract. From the left side of each carcass, individual muscles [longissimus thoracis (LT), gluteus medius, semimembranosus, semitendinosus, biceps femoris, and quadriceps femoris] were collected and weighed. Samples of the longissimus and semitendinosus muscles were immersed in optimal cutting temperature solution, frozen in liquid nitrogen, and then held at −80°C. for subsequent fiber typing. Adipose depots (subcutaneous fat, kidney fat, mesenteric fat) were also collected and weighed. No appreciable subcutaneous fat depots were present in any of the lambs. From the right side of each carcass, all muscle and fat were removed, weighed and ground for total body proximate composition.

**PROXIMATE COMPOSITION**

For proximate analysis, total muscle and fat samples from the right side of each lamb carcass were chopped (Blixer®3 Series D, Robot Coupe Inc., Ridgeland, MS) to reduce particle size. The remaining samples were frozen at −20°C, lyophilized (VirTis, SP Scientific, Warminster, PA), ground (Blixer®3), and stored at −20°C. Duplicate samples were analyzed for nitrogen content by the combustion method using a Leco FP-2000 N analyzer (Leco Corp., St. Joseph, MI) and detector were maintained at 250°C. Duplicate samples were analyzed for nitrogen content by the combustion method using a Leco FP-2000 N analyzer (Leco Corp., St. Joseph, MI) and detector were maintained at 250°C. Fatty acids were quantified by gas chromatography equipped with an Agilent 7673A (Hewlett-Packard, San Fernando, CA) automatic sampler. Separations were accomplished using a 100-m SP2560 (Supelco, Bellefonte, PA) capillary column (0.25 mm i.d. and 0.20 μm film thickness). Column oven temperature increased from 150 to 160°C at 1°C per min, from 160 to 167°C at 0.2°C per min, from 167 to 225°C at 1.5°C per min, and then held at 225°C for 16 min. The detector and detector were maintained at 250°C. Sample injection volume was 1μL. Hydrogen was the carrier gas at a flow rate of 1 mL per min. Samples were run twice with a split ratio of 100:1 for trans C18:1 and long-chain fatty acids, and again at split ratio of 10:1 for conjugated linoleic acid (CLA) and omega-3 fatty acids. Individual fatty acids were identified by comparison of retention times with standards (Sigma, St. Louis, MO; Supelco, Bellefonte, PA; Matreya, Pleasant Gap, PA). Fatty acids were quantified by incorporating an internal standard, methyl tricosanoic (C23:0) acid, into each sample during methylation and expressed as a weight percentage of total fatty acids.

**IMMUNOFLUORESCENCE IMAGE ANALYSIS**

Longissimus and semitendinosus samples were immersed in optimal cutting temperature solution, frozen in liquid nitrogen, and stored at −80°C. Muscle samples were cryosectioned and fiber typed using antibodies for myosin heavy chain (MHC)-fast (AbCam, My-32) and MHC-slow (Hybridoma Bank, BA-F8). The number and cross-sectional area of primary and secondary myofibers were counted on 10 different sections for each lamb, and a ratio of secondary to primary myofibers is reported. The cross-sectional area was measured using IMT iSolution Lite (version 9.4, IMT i-Solutions Inc., Vancouver, BC, Canada).

**STATISTICAL ANALYSES**

Prolactin data were analyzed in a completely randomized design using MIXED procedure of SAS (SAS Inst. Inc., Cary, NC) with treatment, time, and two-way interaction in the model. Gestation length data was also measured using the MIXED procedure with treatment in the model. Ewe was the experimental unit for both analyses. For all lamb data, data were analyzed in a completely randomized design using MIXED procedure with treatment in the model and lamb as experimental unit. Least square means were generated and separated using the PDIF option of SAS. Significance was determined at (P < 0.05).

**RESULTS AND DISCUSSION**

The interaction between day and treatment was significant (P < 0.001) for serum PRL levels (Figure 1). On d 30 of gestation (5 d prior to the initiation of dietary treatments), serum PRL levels did not differ between E+ and E− ewes. At d 50, serum PRL levels in E+ ewes decreased (P < 0.01) from pre-treatment levels (d 30) and were lower (P < 0.01) than E− levels. In E− ewes, serum PRL levels at d 50 were similar to the values at pre-treatment (d 30) and higher (P < 0.01) than E+ ewe values. At d 130, serum PRL levels increased (P < 0.05) in both E+ and E− ewes compared to d 50 levels; however, PRL levels were higher (P < 0.01) for E− than E+. The reduction in serum PRL concentration with exposure to
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FIGURE 1 | Serum prolactin levels in ewes at d 30, 50, and 130 of gestation. Feeding of tall fescue seed was initiated on d 35 and continued through parturition. Treatment × time interaction was significant ($P < 0.0001$).

Ergot alkaloids via grazing endophyte-infected tall fescue pastures or consumption of endophyte-infected tall fescue seed is a classical response observed in sheep (Elsasser and Bolt, 1987; Emile et al., 2000; Parish et al., 2003), cattle (Emile et al., 2000; Watson et al., 2004; Koontz et al., 2012; Stowe et al., 2013), and horses (McCann et al., 1992). It has been documented in multiple species that as parturition approaches maternal serum PRL concentration increases (Chamley et al., 1973; Bryant and Chamley, 1976; Forsyth, 1986) and this increase is hypothesized to be important for maternal lipid metabolism, mammary growth, and milk production and secretion (Hooley et al., 1978; Banchero et al., 2006; Mabjeesh et al., 2013). The levels of PRL reported here for the $E\!-$ group are consistent with previous reports; however, the drastically lower levels observed at d 130 for $E\!+$ could indicate post-partum issues with ewe metabolism and mammary growth, which would negatively impact postnatal lamb growth.

$E\!+$ ewes had approximately 4 d shorter ($P < 0.05$) gestation length than $E\!-$ controls (Figure 2). Similarly, others have reported shorter gestation lengths in ewes with placental insufficiency (Chen et al., 2010) and cows that were nutrient restricted from d 32–83 of gestation (Long et al., 2010). In contrast, horses grazing endophyte-infected tall fescue during gestation have increased gestation lengths (Putnam et al., 1991). Lamb birth weight was reduced ($P < 0.01$) by 37% for $E\!+$ compared to $E\!-$ lambs (Figure 3). Watson et al. (2004) observed a 15% reduction in calf birth weight from cows grazing toxic vs. non-toxic fescue during gestation. These reductions in fetal growth with ergot alkaloid feeding are similar to those reported for high ambient temperature exposure throughout pregnancy, which produces the most severe intrauterine growth restriction (IUGR; Bell et al., 1987, 1989; Thureen et al., 1992; Anthony et al., 2003; Arroyo et al., 2006). In sheep, umbilical blood flow increases throughout pregnancy in order to keep pace with fetal growth during the last half of gestation (Reynolds et al., 1986; Reynolds and Ferrell, 1987; Molina et al., 1991). Fetal growth restriction is highly correlated with reduced uteroplacental growth and development (Reynolds and Redmer, 1995, 2001). Experimental conditions like overnutrition, nutrient restriction, hyperthermia, or high altitude that retard fetal growth also reduce uterine and umbilical blood flows (Reynolds et al., 2006). Because adequate blood flow is essential for normal fetal growth, conditions that restrict fetal and placental growth are associated with reduced rates of placental blood flow and nutrient uptakes by the fetus (Reynolds and Redmer, 1995). Since ergot alkaloids cause vasoconstriction in uterine and umbilical blood flow (Dyer, 1993), these effects would induce fetal growth restriction similar to maternal hyperthermia or nutrient deprivation.

Organ weights (heart, lung, kidneys, spleen, thymus, liver, and pancreas) were also smaller ($P < 0.05$) for $E\!+$ than $E\!-$ (Table 2) except for the pancreas ($P = 0.52$). Total muscle weight from the right side of each carcass was lighter ($P = 0.0093$) for $E\!+$ than

FIGURE 2 | Gestation length (d) of ewes fed tall fescue seed containing endophyte ($E\!+$) vs. endophyte-free ($E\!-$). Treatment was significant ($P = 0.02$).

FIGURE 3 | Lamb birth weight from ewes fed tall fescue seed with endophytes ($E\!+$) vs. endophyte-free ($E\!-$) during gestation. Treatment was significant ($P = 0.001$).
Table 2 | Effect of feeding tall fescue seed with endophyte (E+) vs. endophyte-free (E−) to ewes during gestation (d 35 to parturition) on lamb organ, muscle and adipose tissue weights.

| ORGANS, g | E+ | E− | SEM | P-Level |
|-----------|----|----|-----|--------|
| Heart     | 22.3 | 35.1 | 2.58 | 0.0035 |
| Lungs     | 65.4 | 112.3 | 8.76 | 0.0019 |
| Kidneys   | 16.7 | 24.0 | 1.64 | 0.0067 |
| Spleen    | 4.7 | 9.2 | 1.03 | 0.0081 |
| Thymus    | 4.9 | 11.2 | 2.00 | 0.04 |
| Liver     | 71.6 | 112.5 | 10.2 | 0.017 |
| Pancreas  | 0.84 | 1.3 | 0.050 | 0.52 |
| Total viscera | 234.4 | 311.0 | 29.0 | 0.082 |

MUSCLES, g

| MUSCLES, g | E+ | E− |
|------------|----|----|
| Longissimus | 37.4 | 63.2 |
| Gluteus medius | 11.5 | 17.6 |
| Semitendinosus | 8.5 | 13.6 |
| Semimembranosus | 24.3 | 43.4 |
| Quadriceps femoris | 24.9 | 41.8 |
| Biceps femoris | 17.2 | 29.7 |
| Total muscle | 313.5 | 510.7 |

ADIPOSE, g

| ADIPOSE, g | E+ | E− |
|------------|----|----|
| Mesenteric fat | 4.6 | 5.2 |
| Kidney fat | 12.5 | 19.8 |
| Total adipose | 8.0 | 6.7 |

Table 3 | Effect of feeding tall fescue seed with endophyte (E+) vs. endophyte-free (E−) to ewes during gestation (d 35 to parturition) on lamb organ, muscle and adipose tissue weights as a percentage of body weight.

| ORGANS, % | E+ | E− | SEM | P-Level |
|-----------|----|----|-----|--------|
| Heart     | 0.76 | 0.76 | 0.04 | 0.96 |
| Lungs     | 2.2 | 2.4 | 0.15 | 0.42 |
| Kidneys   | 0.57 | 0.52 | 0.03 | 0.32 |
| Spleen    | 0.15 | 0.19 | 0.02 | 0.07 |
| Thymus    | 0.14 | 0.23 | 0.04 | 0.10 |
| Liver     | 2.3 | 2.4 | 0.10 | 0.40 |
| Pancreas  | 0.24 | 0.027 | 0.009 | 0.81 |
| Total viscera | 8.0 | 6.7 | 0.45 | 0.06 |

MUSCLES, %

| MUSCLES, % | E+ | E− |
|------------|----|----|
| Longissimus | 2.6 | 2.7 |
| Gluteus medius | 0.78 | 0.75 |
| Semitendinosus | 0.89 | 0.57 |
| Semimembranosus | 1.6 | 1.8 |
| Quadriceps femoris | 1.7 | 1.8 |
| Biceps femoris | 1.1 | 1.2 |
| Total muscle | 21.2 | 21.7 |

ADIPOSE, %

| ADIPOSE, % | E+ | E− |
|------------|----|----|
| Mesenteric fat | 0.14 | 0.11 |
| Kidney fat | 0.42 | 0.42 |

Table 4 | Proximate composition of total muscle mass from one side of each lamb carcass from ewes fed tall fescue seed with endophyte (E+) vs. endophyte-free (E−) during gestation (d 35 to parturition).

| ORGANS, % | E+ | E− | SEM | P-Level |
|-----------|----|----|-----|--------|
| Moisture, % | 79.05 | 78.64 | 0.09 | 0.01 |
| Crude protein, % | 17.09 | 18.74 | 0.69 | 0.05 |
| Total Lipid, % | 2.44 | 2.50 | 0.20 | 0.83 |
| Ash, % | 2.12 | 2.17 | 0.77 | 0.78 |

FATTY ACIDS, %

| FATTY ACIDS, % | E+ | E− |
|----------------|----|----|
| C14:0 | 0.90 | 1.01 |
| C16:0 | 19.67 | 20.81 |
| C16:1 cis-9 | 2.14 | 2.03 |
| C17:0 | 0.36 | 0.39 |
| C18:0 | 13.13 | 14.44 |
| C18:1 cis-9 | 49.95 | 49.54 |
| C18:1 cis-11 | 3.03 | 2.99 |
| C18:2 cis-9,12 | 0.65 | 0.51 |
| C18:3 cis-9,12,15 | 0.28 | 0.26 |
| C20:4 cis-5,8,11,14 | 1.89 | 0.61 |
| C20:5 cis-5,8,11,14,17 | 0.40 | 0.18 |
| C22:5 cis-7,10,13,16,19 | 0.31 | 0.50 |
| C22:6 cis-4,7,10,13,16,19 | 0.26 | 0.20 |
| Saturated | 33.70 | 36.26 |
| Monounsaturated | 52.09 | 51.57 |
| Polyunsaturated, n-6 | 2.54 | 1.12 |
| Polyunsaturated, n-3 | 1.25 | 1.16 |
| Ratio of n-6:n-3 | 1.96 | 1.07 |

Total fatty acids, g/100g LT | 1.76 | 1.81 |

Individual muscle weights for LT, semitendinosus, semimembranosus, biceps femoris, quadriceps femoris, and gluteus medius were heavier (P < 0.05) for E− than E+. Kidney fat amounts were lower (P < 0.05) for E+ than E−. Thymus and spleen mass tended (P < 0.10) to be smaller for E+ than E− even when adjusted for body or carcass weight. All other organs and muscle weights did not differ (P > 0.05) when expressed on a weight basis (Table 3). Total viscera weight (weight of the esophagus, rumen, intestines excluding organs) tended to be greater (P < 0.10) for E+ than E− when expressed on a body weight or hot carcass weight basis.

The proximate and fatty acid composition of the total muscle mass from the right side of each lamb carcass is shown in Table 4. Moisture content was higher (P < 0.01) and crude protein content was lower (P = 0.05) in total muscle from E+ than E−. Total lipid and ash content of the muscle did not differ between treatments. Stearic (C18:0) acid concentrations of the total muscle tended to be lower (P = 0.10) for E+ than E−. Arachidonic (C20:4) and eicosapentaenoic (C20:5) acid concentrations were higher (P < 0.05) in total muscle of E+ than E−. Other fatty acid concentrations were not altered by dietary treatment. Total n-6 polyunsaturated fatty acid (PUFA) and the ratio of n-6 to n-3 PUFA were higher (P < 0.05) in the muscle of E+ than E−. Total fatty acid content of the muscle did not differ, which indicates that PUFA fatty acid accumulation in muscle was greater with
E+ exposure. Realini et al. (2005) reported that finishing steers on endophyte-infected vs. endophyte-free tall fescue increased stearic acid and lowered monounsaturated fatty acid concentrations with no change in PUFA. Ailhaud et al. (2008) found that increased levels of n-6 PUFA and a high ratio of n-6 to n-3 PUFA during fetal development in rats stimulated adipogenesis to alter hypertrophy and hyperplasia of adipocytes during postnatal growth. These alterations in fatty acid composition at birth could impact adipogenesis and subsequent adipose tissue deposition.

Lambs exposed to ergot alkaloids in utero had a lower (P < 0.05) secondary to primary muscle fiber ratio in the semitendinosus muscle compared to E− (Figure 4). The ratio of secondary to primary muscle fiber did not differ in the LT. Early prenatal muscle fiber growth is due to hyperplasia of muscle fibers and fiber number is set before birth. Research indicates that muscle fiber hyperplasia is complete by about 70 d of gestation in the pig (Swatland, 1973), 180 d in the cow (Albrecht et al., 2013), and 105 d in the sheep (Du et al., 2010). Intrauterine growth restriction of the fetus during the second trimester of gestation reduces the formation of secondary muscle fibers. The ratio of secondary to primary muscle fibers is reduced with intrauterine crowding in pigs (i.e., runt pig, Aberle, 1984; Pardo et al., 2013) and maternal under-nutrition from d 28 to 78 in sheep (Zhu et al., 2004). Cross-sectional area was also reduced (P < 0.05) in slow and fast-MHC myofibers of the LT and ST muscles in E+ compared to E− (Figure 5). Because postnatal muscle growth is predominately through hypertrophy of existing muscle fibers, a reduction in secondary fiber number also impacts postnatal muscle growth. Pigs that are runts at birth have less total carcass muscle mass and altered adipose tissue cellularity when finished to slaughter weights (Powell and Aberle, 1981). Underwood et al. (2010) found that mid to late nutrient restriction of gestating cows altered growth, adipose, and meat tenderness in the offspring. Long et al. (2012) also reported changes in adipocyte size and carcass parameters in beef offspring from cows with early to mid-gestation undernutrition. Thus, ingestion of ergot alkaloids by ewes during critical time periods of gestation alters fetal muscle growth and development that may have lasting impact on postnatal muscle growth, carcass composition, and palatability throughout the offspring’s lifetime.

These results show that fetal growth is restricted in ewes fed endophyte-infected tall fescue seed to simulate fescue toxicosis syndrome during gestation (d 35 to parturition). This reduction in lamb birth weight with ergot alkaloid exposure is similar to lambs exposed in utero to high ambient temperatures, which is the most severe IUGR. Exposure in utero to ergot alkaloids altered skeletal muscle formation by reducing the ratio of secondary to primary myofibers, myofiber hypertrophy in utero, and protein content of muscles. Due to the number of ruminant animals that graze endophyte-infected tall fescue during gestation, additional research is needed to determine mechanisms by which ergot alkaloids reduce fetal growth and the critical time periods of exposure in order to mitigate its effects on fetal growth.

ACKNOWLEDGMENTS
This research project was supported in part by USDA-NIFA-2010-38942-20745. Appreciation is expressed to M. C. Miller and T. A. Burns for assistance with animal care and sample collection, and N. Korn for myofiber image acquisition. Technical contribution no. 6263 of the Clemson University Experiment Station.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 13 June 2014; accepted: 04 August 2014; published online: 21 August 2014.

Citation: Duckett SK, Andrae JG and Pratt SL (2014) Exposure to ergot alkaloids during gestation reduces fetal growth in sheep. *Front. Chem.* 2:68. doi: 10.3389/fchem.2014.00068

This article was submitted to Chemical Biology, a section of the journal *Frontiers in Chemistry*.

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