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ORIGINAL RESEARCH

Thyroid Hormones and Cortisol Concentrations in Offspring are Influenced by Maternal Supranutritional Selenium and Nutritional Plane in Sheep

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Abstract: To determine the effects of maternal supranutritional selenium (Se) supplementation and maternal nutritional plane on offspring growth potential, ewes were randomly assigned to 1 of 6 treatments in a 2 × 3 factorial arrangement [dietary Se (adequate Se; 9.5 µg/kg body weight vs. high Se; 81.8 µg/kg body weight initiated at breeding) and plane of nutrition [60%, 100%, or 140% of requirements; initiated on day 50 of gestation]]. Lambs were immediately removed from dams at birth and reared. Cortisol concentrations at birth were similar, but by 24 h, a relationship ($P = 0.02$) between maternal Se supplementation and nutritional plane on cortisol concentrations was observed in lambs. A sex of offspring × day of age interaction ($P = 0.01$) and a maternal Se supplementation × nutritional plane × day of age interaction ($P = 0.04$) was observed for thyroxine concentrations. Differences in growth may be influenced by thyroid hormone production early in neonatal life.

Keywords: cortisol; developmental programming; offspring; sheep; thyroid hormones

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Introduction

Maternal influences and investments can drastically alter offspring during development.[1] In humans and livestock, intrauterine growth restricted (IUGR) offspring often experience compensatory growth, with variations in the time required to reach the same level as their contemporaries.[2] This compensatory growth is associated with an increased risk of adiposity and other metabolic and cardiovascular diseases later in the life.[2–4] Specifically, in sheep, our laboratory and others have demonstrated that maternal intake, whether in restriction or excess, can reduce offspring birth weight.[6,7] During prenatal development, suboptimal maternal nutrition is likely to cause significant modifications in developing young. These modifications may alter the overall functionality of the hypothalamic-pituitary-adrenal[7,8] and hypothalamic-pituitary-thyroid axes,[9] and therefore affect cortisol and thyroid hormone regulation, respectively. Changes in the regulation of cortisol and thyroid hormones can impact fetal development, metabolism, and growth trajectory after birth.

Our laboratory recently reported that even when lambs are artificially reared, growth and digestibility are altered by selenium (Se) status and the maternal nutritional plane during gestation.[11] Moreover, in context with the ten principles of developmental programming,[11] sex of the offspring is associated with maternal diet and affects growth rates through 6 mo of life. While weights of offspring are similar at 6 mo of life, body composition differs,[12] reinforcing the concept that compensatory growth may alter metabolic function later in life.

Selenium is necessary for the conversion of thyroxine (T_4) to triiodothyronine (T_3) as well as for overall thyroid function.[13,14] When supranutritional levels of Se are provided to dams throughout gestation, fetal weights increase.[15] Additionally, intake of specific nutrients, such as Se, may be suboptimal or excessive because of regional soil and feedstuff variability.[16] Because Se has many important antioxidant and metabolic roles,[17] supranutritional Se may have positive effects during gestation, particularly in situations in which ewes are metabolically or nutritionally stressed. Additionally, Se status may offset some of the negative impacts of nutrient restriction by enhancing overall metabolic function in the fetus.

There have been no studies to investigate the effects of maternal Se supplementation and nutritional plane on offspring cortisol and thyroid hormone production. We hypothesized that since maternal nutrition during pregnancy alone impacted birth weight and offspring growth, it may also influence endocrine patterns in offspring. The objective of the current study was to determine how maternal supranutritional Se supplementation and nutritional plane affect cortisol and thyroid hormone production in offspring through 180 d of life.

Materials and Methods

Animals and diets

Animal care and use was approved by the Institutional Animal Care and Use Committees at North Dakota State University, Fargo, and the USDA-ARS, US Sheep Experiment Station (USSES), Dubois, ID, USA. A full description of the breeding and feeding programs has been published previously.[10,18] Briefly, at the USSES, 160 Rambouillet ewe lambs (age, 240 ± 17 d) were randomly assigned to Se treatment at breeding. Selenium treatments were adequate Se (ASe; 9.5 μg/kg body weight, BW) vs. high Se (HSe; 81.8 μg/kg BW) from Se-enriched yeast (Diamond V, Cedar Rapids, IA, USA), and were delivered in pellet form as a daily top dressing (100 g/ewe). During breeding through pregnancy diagnosis (~33 d post-breeding) ewes were fed a diet (2.04 kg/ewe daily) consisting of 47% alfalfa hay, 20% corn, 20% sugar beet pulp pellets, 8% malt barley straw, and 5% concentrated separator byproduct (DM basis).[10,18] Eighty-two pregnant ewes (40 and 42 ewes in the ASe and HSe treatments groups, respectively) were identified and shipped (1,544 km; ~14 h) to the Animal Nutrition and Physiology Center at NDSU for experiments.

Upon arrival at NDSU, ewes remained on their assigned Se treatments and were individually housed in 0.91 × 1.2-m pens in a temperature-controlled (12 °C) and ventilated facility for the duration of the study. Lighting within the facility was automatically timed to mimic daylight patterns. On d 50 of gestation, ewes were assigned randomly to 1 of 3 nutritional diets: 60% (RES), 100% (CON), or 140% (HIGH) of the National Research Council (NRC) requirements,[19] resulting in a randomized design with a 2 × 3 factorial arrangement of treatments [ASe-RES (n = 14); ASe-CON (n = 13); ASe-HIGH (n = 13); HSe-RES (n = 14); HSe-CON (n = 14); HSe-HIGH (n = 14)]. All diets were fed once daily in a completely pelleted form consisting of 36% beet pulp, 22% alfalfa meal, 16% ground corn, 18% soybean hulls, and 5% to 7% soybean meal (0.48 cm diameter).[18] Soybean meal was reduced to 5% in the high Se pellet to accommodate addition of 2% Se-enriched yeast.[18] Ewes had free access to water and a trace mineralized salt block (containing no added Se; American Stockman, Overland Park, KS, USA). As with diets fed at USSES, those fed at NDSU were formulated to be similar in metabolizable energy (ME) and protein and to meet or exceed other nutrient requirements.[18,19] A nutritional plane was achieved by proportional downward (RES) or upward high (HI) shifts in dietary intake, resulting in global shifts in total nutrients supplied. Individual daily allotments of diets were usually completely consumed, with the appearance of orts being rare. Targeted ME requirements for CON-fed animals were based on NRC recommendations[19] for 60-kg BW, pregnant ewe lambs during mid to late gestation (ADG of 140 g/d), and were adjusted to 2.36 Mcal of ME/d based on previous experience for this type of ewe consuming similar diets housed in the Animal Nutrition and Physiology Center at NDSU. Supply of ME required per ewe was then adjusted by adding or subtracting 0.0198 Mcal of ME/kg of BW above or below the initial 60-kg BW target. Daily dry matter intake for individual ewes of the respective diets was then determined based on ME demand and dietary ME composition.[18] Because ASe and HSe pelleted diets were similar in ME (2.63 and 2.64 Mcal of ME/kg respectively), Se targets for HSe treatments were met by blending ASe and HSe pellets. Body weight was measured every 14 d, and the diets were adjusted accordingly.

Parturition and postnatal procedures

Postnatal procedures have been previously described.[10] Briefly, all births were allowed to occur spontaneously and were observed so that lambs could be immediately removed from their dams. All lambs were reared similarly in a temperature-controlled (21 °C) and ventilated facility for the duration of the study. At birth, a blood sample was obtained from each lamb from the jugular vein and lambs were weighed. Lambs were fed artificial colostrum for the first 20 h (19.1 mL/kg first two feedings and 25.5 mL/kg subsequent feedings to achieve 10.64 g IgG/kg BW) followed by feeding of milk replacer (Super Lamb Milk Replacer; Merrick's Inc., Middleton, WI, USA) and adapted to a teat bucket system with access to fresh alfalfa leaves, creep feed, and water. From 24 h post-partum to weaning, lambs were allowed access to milk replacer and feed ad libitum. Male lambs were castrated and all lambs were tail docked at 7 d of age. Lambs were weaned to a totally pelleted grower diet at 57 ± 3.8 d of age and transitioned to a finisher diet at 116 ± 3.9 d of age.[10]

Lambs were weighed at birth and on d 1, 7, 21, 35, 49, 57, 78, 99, 120, 141, 162, and 180. Lamb weights and average daily gain have been previously published.[10] To determine the relative weight gain per individual, the percentage change in lamb weight from birth was calculated. At 24 h postpartum and on d 7, 21, 35, 49, 57, 78, and 180 (prior to sacrifice), a blood sample was taken from the jugular vein of each lamb. Blood samples (10 mL) were collected into sterile evacuated nonheparinized tubes (Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ, USA). Serum was obtained by centrifugation (1,500 × g for 30 min) and stored at −20 °C until further analysis.

Necropsy

At 180 ± 2.2 d of age, lambs were weighed, stunned by captive bolt (Supercash Mark 2, Acceles and Shelvoke Ltd., UK), and exsanguinated. Complete necropsy was performed, including removing digesta from the gastrointestinal tract. Adrenal glands and thyroid glands were removed from each lamb and weighed. Empty body weight was calculated as final body weight minus total digesta weight. To express organ mass on an empty body weight basis, fresh organ mass (g) was divided by empty body weight (kg).

Cortisol analysis

Serum samples were analyzed for cortisol concentration as previously described.[20] Briefly, serum samples (10 μL) were assayed in duplicate using a chemiluminescence immunoassay (Immulite 1000, Siemens, Los Angeles, CA, USA). Within each assay, lesser-, medium-, and greater-cortisol pools were assayed in duplicate. Intra- and interassay coefficients of variation (CV) were 7.5% and 6.7%, respectively. Due to the elevated concentrations of cortisol at birth and 24 h after birth, these time periods were analyzed separately from d 7 to 180.

Thyroid hormone analysis

T_4 and T_3 concentrations were determined using the chemiluminescence immunoassay using the Immulite 1000 (Siemens), utilizing components of commercial kits (Diagnostic Products Corp, Los Angeles, CA, USA) as previously described.[21] Within each assay, lesser-, medium-, and greater-T_4 and T_3 pools were assayed in duplicate. Fifteen-microliters and 25-µL serum samples were assayed in duplicate for T_4 and T_3, respectively. Intraassay CVs were 3.5% and 6.2% for T_4 and T_3, respectively, and the interassay CVs were 5.2% and 7.2% for T_4 and T_3, respectively.

Statistical analysis

The experimental design for this study was a completely randomized design with a 2 × 3 factorial arrangement of treatments. Individual lambs served as experimental units since ewes were individually penned with treatment imposed in utero. Data were analyzed using both MIXED and GLM procedures of SAS Statistical Software (SAS Inst. Inc., Cary, NC, USA). Models contained effects for level of Se (ASe and HSe), nutrition (RES, CON, and HIGH), sex of offspring, and all interactions. For the variables cortisol, T_4, and T_3, an unstructured covariance structure was used. As ewes carried both singletons (n = 69) and twins (n = 8 sets), litter size was used as a covariate in the model. Means were separated by least significant difference. Interactions and main effects were considered significant when $P \leq 0.05$. Only significant interactions or main effects are shown in the results.

Results

Birth weights

Birth weights of lambs in this study have been previously reported.[10] Briefly, while maternal Se supplementation did not influence birth weight, there was a maternal plane of nutrition by sex of offspring interaction. Males from RES- (3.78 ± 0.19 kg) and HIGH- (3.50 ± 0.20 kg) fed ewes were lighter at birth than males from CON-fed (4.31 ± 0.19 kg) ewes. Females from RES-fed (3.32 ± 0.15 kg) ewes were lighter than from CON-fed (3.96 ± 0.17 kg) ewes, with those from HIGH (3.94 ± 0.18 kg) being intermediate. Moreover, female lambs were lighter than male lambs from RES-fed ewes, while no sex differences were apparent in CON and HIGH-fed ewes.[10]

Cortisol

Serum cortisol concentrations at birth were not affected ($P > 0.28$) by maternal plane of nutrition and averaged 169.2 ± 5.4 ng/mL. By 24 h after birth, an interaction ($P = 0.02$) was observed between maternal Se supplementation and nutritional plane on cortisol concentrations in lambs (Fig. 1). In lambs from ASe ewes, those from RES-fed ewes generally showed ($P = 0.06$) increased cortisol compared to CON-fed with HIGH-fed being intermediate. In lambs from HSe ewes, RES-fed showed decreased ($P < 0.05$) cortisol compared with CON-fed with those from HIGH-fed being intermediate. Cortisol levels from lambs of RES and HIGH-fed ewes were not influenced by Se supplementation, while lambs from HSe-CON showed increased ($P = 0.03$) cortisol compared to ASe-CON (Fig. 1).

Maternal Se supplementation, nutritional plane, or their interactions did not have an effect ($P \geq 0.61$) on cortisol concentrations in lambs from days 7 to 180. There was a tendency ($P = 0.06$) for wethers to show increased cortisol concentrations compared to female lambs from 7 to 180 d of age (14.38 vs. 12.51 ± 0.71 ng/mL). However, there was an effect ($P < 0.001$) of day on serum cortisol concentrations from d 7 to 180 (Fig. 2). Cortisol concentrations decreased from d 7 to 35 and remained steady through d 59. Thereafter, the concentrations increased to d 78 and dropped to concentrations observed on d 59 to d 180.

Thyroid hormones

There were no effects ($P \geq 0.13$) of maternal Se supplementation, nutritional plane, sex of offspring or their interaction on T_3 or T_4 concentrations at birth, which averaged 3.4 ± 0.1 ng/mL for T_3 and 105.5 ± 35.2 ng/mL for T_4. From d 7 to 180, day ($P < 0.001$) affected T_3 concentrations (Fig. 3). Concentrations of T_3 continued to decline from d 7 to 58, which were similar to those on d 78, and then further decreased to its lowest concentration at d 180. There was a sex of offspring × day of age interaction on T_4 concentrations (Fig. 4). At 21 d of age, female lambs had greater ($P = 0.02$) T_4 concentrations than male lambs. Additionally, a maternal Se supplementation × nutritional plane by day of age interaction ($P = 0.04$) on T_4 concentrations was observed in the offspring (Fig. 5A). Generally, concentrations of T_4 increased from d 7 to 35,

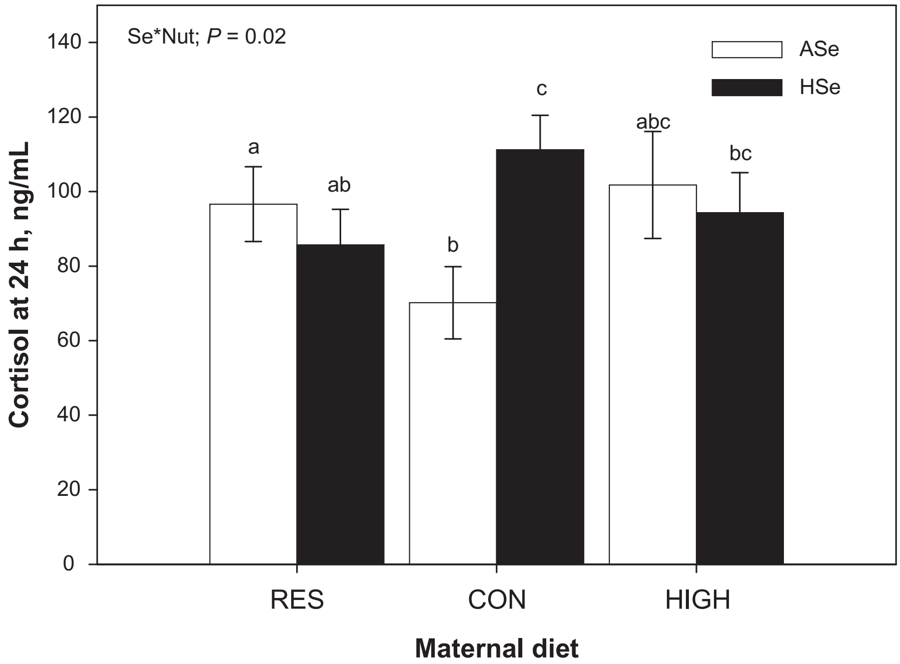

Figure 1. Cortisol concentrations at 24 h of life in lambs from ewes receiving either adequate selenium (ASe; white bars) or high selenium (HSe; black bars) in control (CON; 100% NRC recommendations), restricted (RES; 60% of CON), or overfed (HIGH; 140% of CON) diets.
Note: [abc]Means ± SEM with different superscripts differ, $P \leq 0.05$.

decreased by d 78, and either remained similar or increased by 180 d of age (Fig. 5A). In offspring from ASe ewes, on d 7, lambs from RES-fed ewes showed greater T_4 concentrations than those from HIGH-fed ewes. Thereafter, T_4 concentrations were stable. For lambs from HSe ewes, while T_4 concentrations were similar on d 7, lambs from HIGH-fed ewes decreased ($P \leq 0.03$) T_4 compared to lambs from RES-fed and CON-fed ewes, which did not differ ($P = 0.60$) by d 21. By d 35, lambs from RES-fed ewes generally

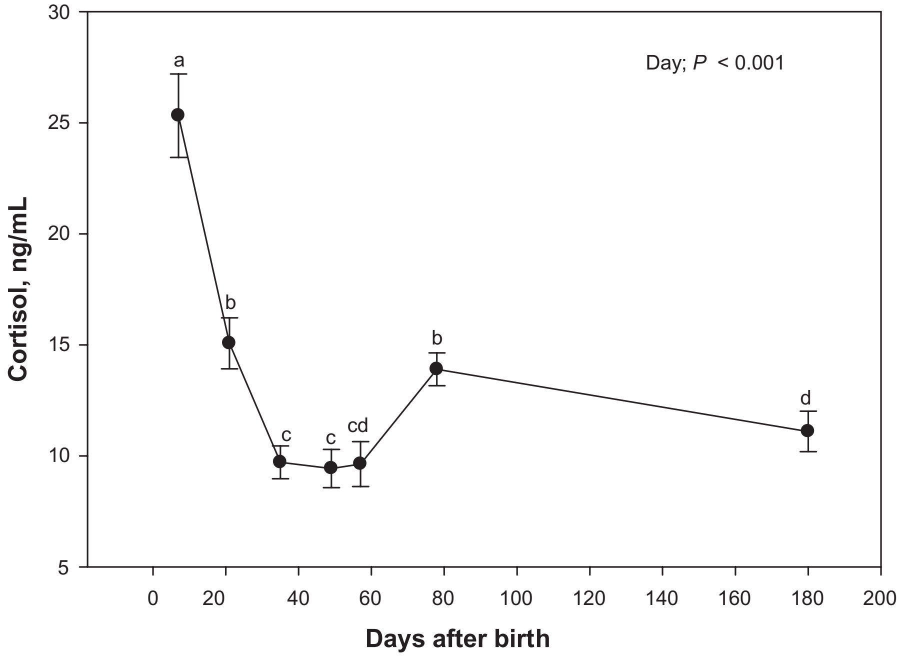

Figure 2. Offspring cortisol concentrations from day 7 until 180.
Note: [abcd]Means ± SEM with different superscripts differ, $P \leq 0.05$.

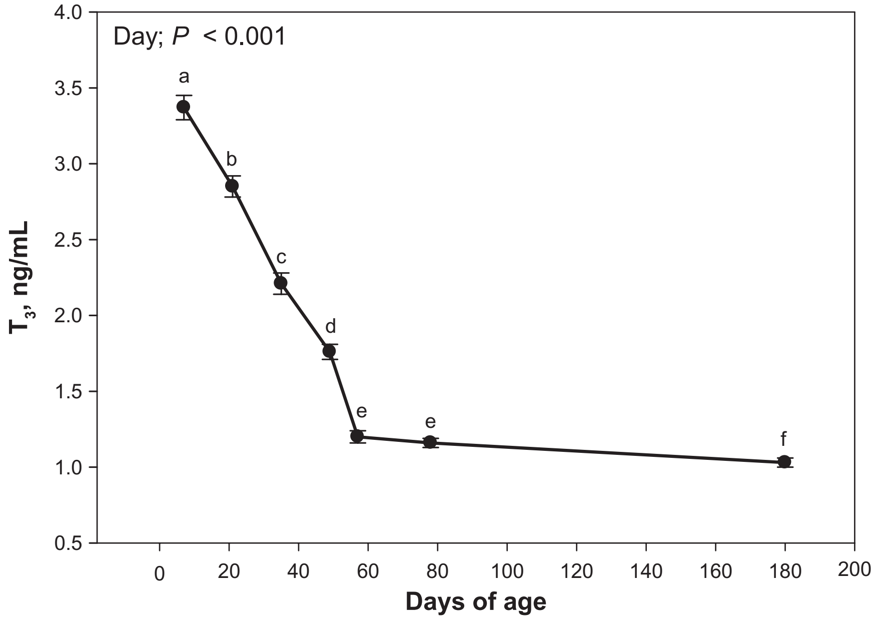

Figure 3. Offspring concentrations of T_3 from day 7 to 180.
Note: [abcdef]Means ± SEM with different superscripts differ, $P \leq 0.05$.

showed increased T_4 ($P \leq 0.09$) compared to CON and HIGH-fed ewes, which did not differ ($P = 0.94$). Thereafter, T_4 concentrations remained similar until d 180, while lambs from RES-fed ewes generally showed increased T_4 ($P = 0.08$) compared to CON-fed, with HIGH-fed showing intermediate values. Within the lambs from RES-fed ewes, T_4 concentrations were generally greater on d 21 in HSe vs. ASe ewes ($P = 0.06$), and were greater at 180 d of age (Fig. 5D). In lambs from CON-fed and HIGH-fed ewes, HSe showed greater T_4 concentrations than ASe on d 7 ($P \leq 0.04$). Regardless of maternal Se status, T_4 concentrations were similar through d 180 in lambs from CON-fed ewes. However, in lambs from HIGH-fed

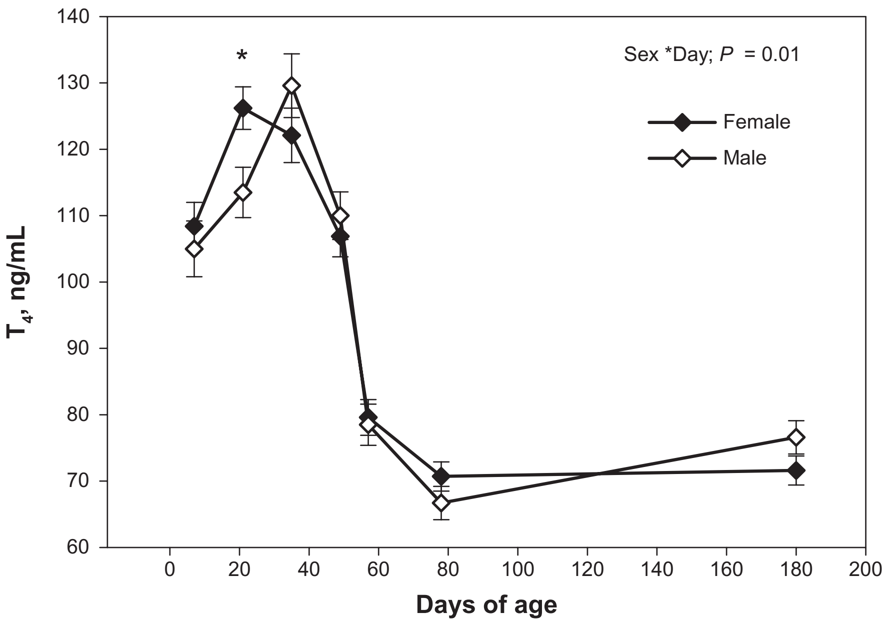

Figure 4. Thyroxine concentrations in female (black diamonds) and male (white diamonds) lambs from day 7 to 180.
Note: *Means ± SEM on day 21 differ, $P < 0.05$.

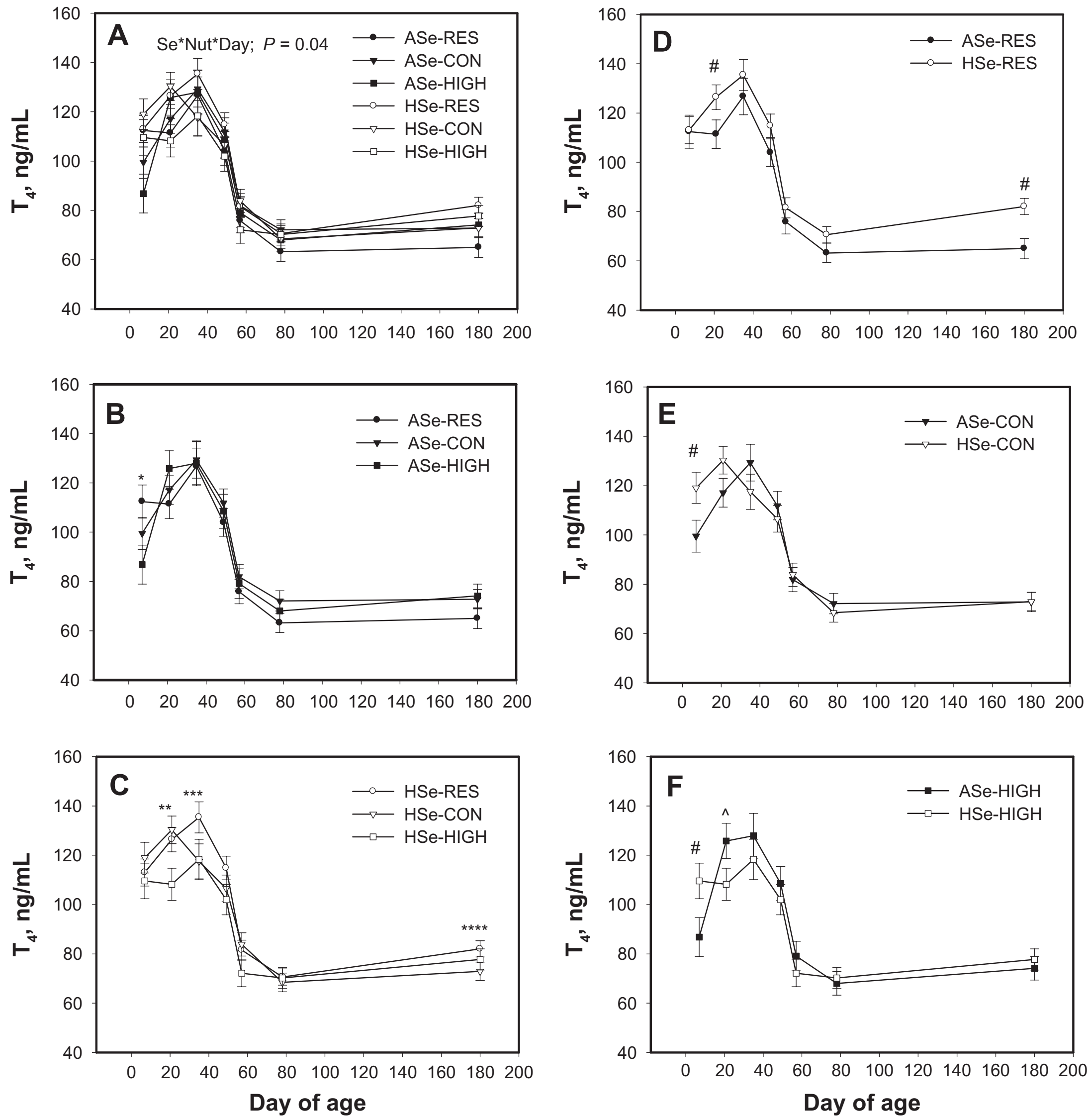

Figure 5. Thyroxine concentrations from day 7 until 180 were affected by an interaction between maternal nutritional plane [CON = 100% of NRC recommendations (triangles); RES = 60% of NRC recommendations (circles); HIGH = 140% of NRC recommendations (squares)], selenium status [adequate selenium (ASe; black) and high selenium (HSe; white)], and day of age (**A**). Lambs from ASe ewes with differing nutritional planes (**B**), HSe ewes with differing nutritional planes (**C**) are depicted. Moreover, data to compare lambs from ASe and HSe ewes within RES (**D**), CON (**E**), and HIGH (**F**) nutritional planes are shown in the right hand panel.

Notes: *RES > HIGH, $P = 0.02$; **RES and CON > HIGH, $P \leq 0.03$; ***RES tends > CON, $P = 0.07$; ****RES tends > CON, $P = 0.08$; #HSe > ASe, $P \leq 0.05$; ^ASe > HSe, $P = 0.07$.

ewes, HSe treatment showed lower T_4 concentrations than in the lambs from the ASe ewes on d 21 ($P = 0.07$). From d 35 to 180, T_4 concentrations were similar in lambs from ASe and HSe HIGH-fed ewes.

Growth

While there was no main effect or interactions with maternal Se supplementation ($P \geq 0.23$), there was an interaction ($P = 0.004$) among maternal nutrition, sex, and day on percentage weight change from birth (Fig. 6A). Females from RES-fed ewes exhibited markedly greater ($P < 0.05$) percentage weight gain compared to female lambs from CON-fed and HIGH-fed ewes from d 120 to 180 (Fig. 6B). Within lambs from RES-fed ewes, female exhibited an increased percentage weight gain than males at d 78 to 162 and again on d 180 ($P < 0.05$) (Fig. 6D). In male lambs from HIGH-fed ewes, percentage weight gain by d 99 and 120 was greater compared to male lambs from RES-fed and CON-fed ewes which were similar ($P < 0.05$) (Fig. 6C). However, by d 162, male lambs from RES-fed ewes had an increased percentage

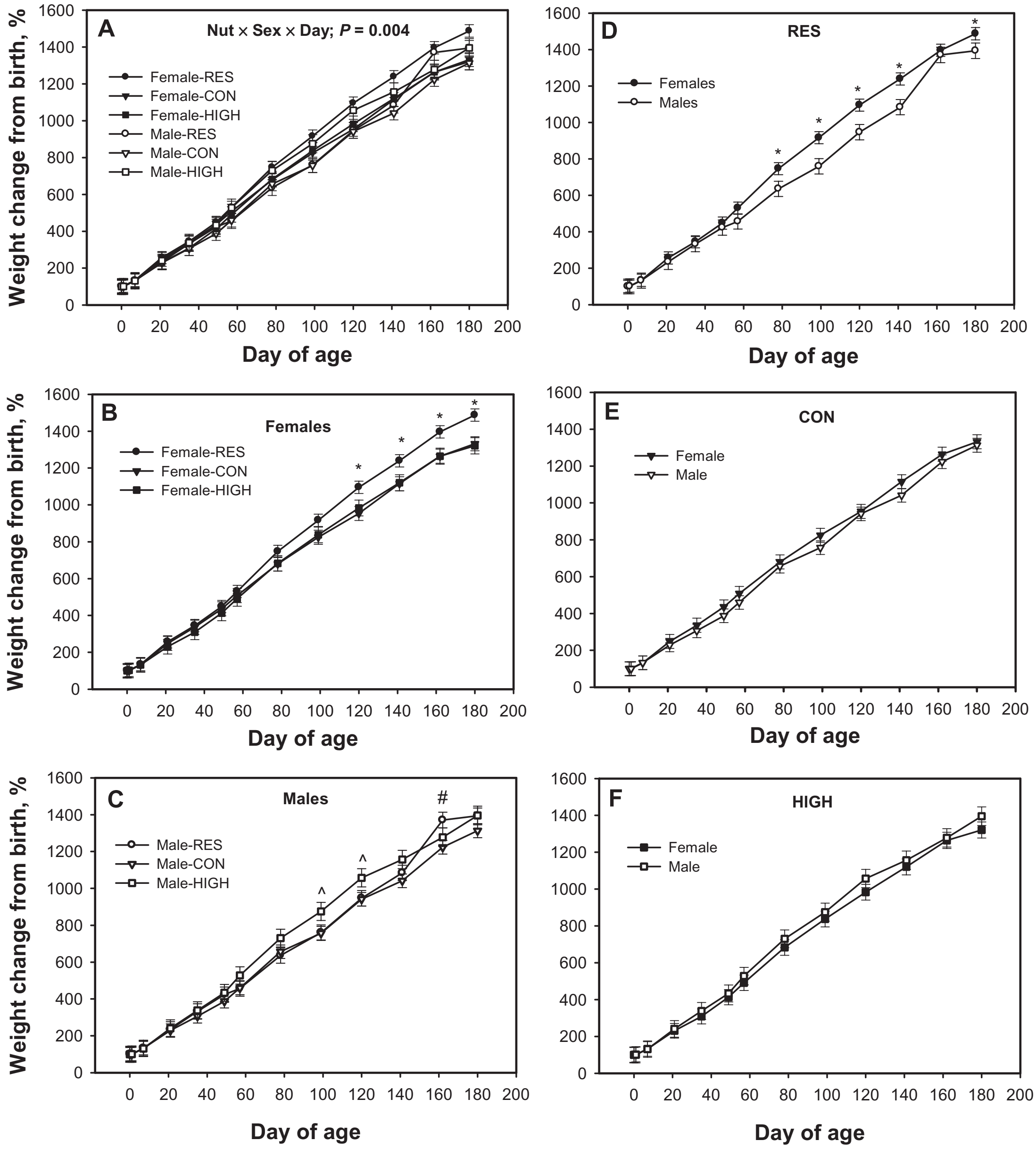

Figure 6. Percentage weight gain from birth was affected by an interaction between maternal nutritional plane, offspring sex, and day of age (**A**; $P = 0.004$). Female (**B**) and male (**C**) born from ewes fed 60% (RES), 100% (CON) or 140% (HIGH) of NRC recommendations are depicted. Moreover, to compare male and female percentage weight change from birth in RES (**D**), CON (**E**), and HIGH (**F**) fed ewes, data are shown in the right hand panel.
Notes: *LSMeans ± SEM within a day differ, RES > CON = HIGH (B); RES-female > RES-males (D); $P < 0.05$. In (C), ^LSMeans ± SEM within a day differ, HIGH > RES = CON; ≤LSMeans ± SEM within a day differ, RES > CON; HIGH is intermediate.

weight gain compared to males from CON-fed ewes, ($P = 0.05$) (Fig. 6C), with males from HIGH-fed ewes showing intermediate values. There was no statistical difference between percentage weight change from birth in male and female lambs born from CON-fed (Fig. 6E) and HIGH-fed (Fig. 6F) ewes.

Adrenal and thyroid gland weight

Adrenal gland weight and adrenal gland weight per empty body weight were not affected ($P \geq 0.13$) by maternal plane of nutrition, maternal Se status, sex of the offspring, or their interactions and averaged 2.29 ± 0.06 g and 0.050 ± 0.001 g/kg.

There was an interaction ($P \leq 0.04$) between maternal Se status, nutritional plane, and sex of the offspring on thyroid weight (g and g/kg; Table 1). Female lambs from ASe-HIGH ewes had an increased thyroid weight compared to female lambs from HSe-HIGH ewes ($P = 0.04$). Moreover, female lambs from ASe-HIGH ewes tended to have larger thyroids than male

Table 1. Impact of maternal Se supplementation, nutritional plane, and sex of offspring on thyroid weight (g and kg^{-1} in offspring at 180 d of age.

	Female	Male	SEM	*P*-value Se × Nut × Sex
Thyroid, g				
ASe				0.03
RES	2.66	2.64	0.35	
CON	2.39	2.70	0.34	
HIGH	3.26[ax]	2.21[b]	0.41	
HSe				
RES	2.89	2.82	0.41	
CON	2.93	2.43	0.31	
HIGH	2.24[y]	3.22	0.58	
				***P*-value**
Thyroid, g/kg				
ASe				0.04
RES	0.061	0.056	0.006	
CON	0.056	0.053	0.006	
HIGH	0.074[cx]	0.050[d]	0.008	
HSe				
RES	0.063[†]	0.057	0.006	
CON	0.062[c]	0.048[d,†]	0.008	
HIGH	0.051[y]	0.071	0.012	

Notes: [1]Calculated as g of thyroid divided by kg of empty body weight. [ab]LSMeans ± SEM between sexes tend to differ; $P = 0.07$. [cd]LSMeans ± SEM between sexes differ; $P \leq 0.05$. [xy]LSMeans ± SEM within a sex differ; $P \leq 0.04$. [†]LSMeans ± SEM across nutritional plane and sex differ; $P = 0.05$.

lambs from ASe-HIGH ewes ($P = 0.07$). When thyroid weight was divided by empty body weight (g/kg), female lambs from ASe-HIGH ewes had increased mass compared to female lambs from HSe-HIGH ewes ($P = 0.02$). Moreover, female lambs from ASe-HIGH ewes had larger relative thyroid mass (g/kg) than male lambs from ASe-HIGH ewes ($P = 0.04$). In lambs from HSe-CON ewes, females had a larger ($P = 0.01$) relative thyroid mass compared to males.

Discussion

We found that the maternal plane of nutrition and supranutritional Se supplementation does not impact cortisol, T_3, or T_4 concentrations immediately at birth. Due to the extremely high concentrations of cortisol at birth, no maternal dietary effects were observed. However, by 24 h, an interaction between Se and maternal nutrition was observed. Maternal undernutrition increased cortisol production in newborn lambs by more than in controls in ASe ewes. In lambs from dams fed HSe, cortisol concentrations were greater in lambs from CON-fed compared with undernourished dams. Overnutrition did not influence cortisol by 24 h in newborn lambs. After 24 h, cortisol concentrations were not influenced by maternal diet or sex of the offspring.

Observed changes in cortisol concentrations over time can most likely be explained by lamb development and maturation. Since cortisol is necessary for proper organ development, particularly lung development, high concentrations should be present at birth. However, prolonged elevated levels of cortisol have deleterious effects, and therefore a decrease in cortisol concentrations is crucial for proper growth, protection of developing tissues, and maintenance of a healthy immune system.[23,24] After being "weaned" from teat bucket units, all lambs were introduced to more solid food. This alteration in diet may have caused the increase in cortisol from d 57 to 78.

Since thyroid hormones are also important for proper development and can be deleterious when chronically elevated, it is not surprising that the biologically relevant form of the hormone, T_3, followed a similar pattern to cortisol concentrations as the lambs grew. Selenium is known to participate in the conversion of T_4 to T_3[24] through selenoprotein type 1 iodothyronine 5-deiodinase.[25] In this study, we observed increases in T_4 concentrations in lambs from HSe ewes consuming similar diets as ASe ewes during early life (d 7 to 21). Interestingly, T_3 concentrations were not influenced by Se supplementation. Previous studies have reported that thyroid hormone concentrations from fetuses are reduced during hypoxemic conditions associated with IUGR. DeBlasio et al[26] suggested that placental restriction and small body size at birth may increase activation of T_4 to T_3 and sensitivity of soft tissue to thyroid hormones, which may contribute to the accelerated offspring growth following IUGR pregnancies. We previously reported maternal Se supplementation did not impact birth weight or placental weight; however, both RES-fed and HIGH-fed ewes had lighter lambs.[18] Moreover, we reported that lambs from HIGH-fed ewes generally have decreased cotyledonary weight compared to RES-fed.[18] Concentrations of T_3 were unaffected, although T_4 concentrations differed by maternal Se supplementation, plane of nutrition, and sex of the offspring. This indicates that the conversion to T_3 was not affected. Moreover, compensatory growth in our lighter lambs at birth may have been due to enhanced conversion of T_4 to T_3, allowing for similar weights at 180 d of age. Females from RES-fed ewes may have been experiencing a period of compensatory growth possibly due to IUGR. Additionally, these females had the lowest birth weights, supporting this hypothesis since IUGR can be characterized by restriction in fetal growth due to an insufficient placenta, resulting in low birth weights, and altered postnatal growth.[26] The pattern of growth for all males was also interesting, but unfortunately not as easy to address.

Lastly, it would have been ideal if individual feed intake of each lamb was measured. Having individual feed intake would have allowed us to more accurately conclude the mechanisms for differences observed in endocrine profiles and rate of gain. Modification of feeding behavior is highly likely, as others have reported that maternal diet can impact this.[27] However, since we were managing all lambs independent of the dam throughout the experiment, it was not logistically feasible to collect that data in this current study. However, feed intake is an important measurement that should be assessed in future studies.

In conclusion, maternal nutrition during pregnancy alone impacts endocrine patterns in the offspring. Maternal Se supplementation and plane of nutrition can influence multiple parameters of lamb development. There was minimal influence of treatments on cortisol and T_3 production over the offspring's lifespan. While there were few differences in these hormone concentrations, it remains beneficial to monitor growth and development throughout life.

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Author Contributions

Conceived and designed the experiments: KAV, LPR, CJH, DAR, JSC. Analysed the data: KAV, LAL, TLN. Wrote the first draft of the manuscript: LAL, KAV. Contributed to the writing of the manuscript: KAV, TLN, LAL, CJH, JSC. Agree with manuscript results and conclusions: KAV, TLN, LAL, LPR, CJH, DAR, JSC. Jointly developed the structure and arguments for the paper: KAV, TLN, JSC, LPR, DAR. Made critical revisions and approved final version: KAV, TLN, LAL, LPR, CJH, DAR, JSC. All authors reviewed and approved of the final manuscript.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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