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Early prenatal androgen exposure reduces testes size and sperm concentration in sheep without altering neuroendocrine differentiation and masculine sexual behavior

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ABSTRACT

Prenatal androgens are largely responsible for growth and differentiation of the genital tract and testis and for organization of the control mechanisms regulating male reproductive physiology and behavior. The aim of the present study was to evaluate the impact of inappropriate exposure to excess testosterone (T) during the first trimester of fetal development on the reproductive function, sexual behavior, and fertility potential of rams. We found that biweekly maternal T propionate (100 mg) treatment administered from Day 30–58 of gestation significantly decreased ($P < 0.05$) postpubertal scrotal circumference and sperm concentration. Prenatal T exposure did not alter ejaculate volume, sperm motility and morphology or testis morphology. There was, however, a trend for more T-exposed rams than controls to be classified as unsatisfactory potential breeders during breeding soundness examinations. Postnatal serum T concentrations were not affected by prenatal T exposure, nor was the expression of key testicular genes essential for spermatogenesis and steroidogenesis. Basal serum LH did not differ between treatment groups, nor did pituitary responsiveness to GnRH. T-exposed rams, like control males, exhibited vigorous libido and were sexually attracted to estrous females. In summary, these results suggest that exposure to exogenous T during the first trimester of gestation can negatively impact spermatogenesis and compromise the reproductive fitness of rams.

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1. Introduction

Dogma holds that mammalian embryos develop a female phenotype unless they are exposed to testosterone (T), which causes them to develop a male phenotype. Prenatal T also masculinizes brain functions that control sexually dimorphic gonadotropin secretion, sexual behaviors, and brain morphology. These effects are permanent and limited to critical periods early in life. Inappropriate androgen exposure during development has deleterious consequences in adult females. In humans, daughters born to hyperandrogenic mothers having polycystic ovarian syndrome (PCOS) or congenital adrenal hyperplasia (CAH) or girls born with classic CAH are at risk of having polycystic ovaries, impaired fertility, and masculinized genitalia and behaviors [1–3]. Animal studies suggest that prenatal androgen excess produces reproductive dysfunctions in female offspring that culminate in infertility [4–8]. The reproductive defects associated with experimental

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gestational hyperandrogenism in females include, elevated serum androgen levels, reduced steroid negative feedback sensitivity, disrupted estrogen-positive feedback, increased LH secretion, and the development of multifollicular ovaries.

It has not been firmly established whether there is an altered male reproductive phenotype associated with prenatal androgen excess. However, sperm counts and fertility are reduced in men with classic CAH [3,9], and Sertoli cell function may be altered in sons of women with PCOS [10]. In adult male rats and sheep, excess prenatal T exposure reduces testes size, numbers of germ cells, sperm counts and motility, and serum T concentrations [11–13]. The exact mechanisms for these effects are not understood but have been associated with anatomical [14] or paracrine disruptions to the testis [15–17]. Prenatal androgen excess also affects the central control of reproduction in male sheep by altering FSH, LH, and T responsiveness to a GnRH agonist [15,18] or by altering hypothalamic release of GnRH [19,20]. Finally, genital reflexes, copulatory behaviors, and sexual partner preferences are altered in male rats and ferrets exposed to excess levels of T prenatally [21–24].

Previous studies in sheep evaluated the effects of excess prenatal androgen exposure for long durations on male reproduction. Lower doses and shorter durations of androgen exposure are known to produce females with varying degrees of genital virilization and alterations of the hypothalamic-pituitary-gonadal axis [25]. Few studies have evaluated the effects of limiting the timing of exposure in males to the early part of the critical period when the gonads and genitalia differentiate, and functional connections are established between the hypothalamus and pituitary [26,27]. We reported that early exposure to exogenous T between Days 30 and 60 of gestation (term = 147 d) acutely suppresses LH secretion and Leydig cell steroidogenesis in a manner consistent with enhanced negative feedback but found that hypothalamic gene expression is altered even after exposure ended [12]. Early excess T also paradoxically reduced the volume of the ovine sexually dimorphic nucleus, which is correlated with sexual partner preferences in sheep [28]. The objective of the present study was to investigate whether early excess T exposure has enduring effects on the reproductive function, sexual behavior, and potential fertility of adult rams. We hypothesized that early excess androgen exposure would disrupt the normal trajectory for development of the reproductive system leading to significant deficits in clinically based fertility parameters, impaired hormone responses and sexual behaviors in sexually mature rams. We also expected that prenatal T-treatment would alter the expression of specific testicular genes that regulate T synthesis and spermatogenesis. Our results showed that early prenatal androgen exposure significantly reduced testes size and sperm concentration in sheep without altering testicular cell numbers, neuroendocrine differentiation, and masculine sexual behaviors.

2. Material and methods

2.1. Experimental animals and treatments

Thirty Polypay ewes (*Ovis aries*) were bred at the sheep facility at Oregon State University. Animal husbandry and experimental protocols were conducted according to the principles and procedures specified by the Public Health Service Policy on Humane Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of Oregon State University.

Mature ewes were mated during the breeding season after they underwent estrous cycle synchronization using intravaginal progesterone treatments given by a controlled internal drug release (CIDR) device (Zoetis, New York, NY) followed by a prostaglandin F2α injection as described previously [29]. Pregnant ewes were assigned randomly to control (n = 14) and T propionate (TP) treatment (n = 17) groups and received twice weekly i.m. injections of either corn oil vehicle or 100-mg TP (Steraloids, Newport, RI) from Day 30 to 58 of gestation. This androgen dose and regimen has been found previously to masculinize the external genitalia and affect the timing of puberty in female sheep [30] and produces concentrations of T in the fetus approximately equal to twice that of control male fetuses [31,32].

Lambs were born between late February and early April. There were 23 control (C) lambs (male = 12; female = 11) and 26 TP-exposed (T) lambs (male = 15; female = 11). One T male died soon after birth and was not included in any analysis or summary data. The lambs were weighed at birth and periodically thereafter. Jugular blood samples were drawn for hormone measurements within the first 24 h after birth and then again at 9 mo. Crown-rump, anogenital (AGD), and anoumbilical (AUD) measurements were also recorded at birth and 1 mo of age. Scrotal circumference was measured at birth, 1, 7, 9, 12, and 20 mo of age. Male offspring were studied from pregnancies where at least one male was present: 9 C pregnancies (2 single, 7 twin, and 1 triplet litters) and 12 T pregnancies (6 single, 5 twin, and 1 triplet litters). Of both the C and T pregnancies, one twin pair and the triplet set were males. C females were used as controls in the subsequent estrogen challenge and receptivity tests. T females were not studied after they were born. C and T-exposed lambs were raised together and weaned at 90 d of age after which they were separated by sex in nonadjoining pastures with ad libitum access to grass, water, and mineral supplements. During the winter, they were fed alfalfa hay supplemented with a barley-based concentrate. The sheep were regularly treated with antihelminthics to control internal parasite infestation.

2.2. GnRH challenge

Serum LH responses to GnRH administration were evaluated to determine whether excess prenatal exposure to T altered anterior pituitary sensitivity in T rams compared to C rams. The test was conducted in testes-intact rams at ~7 mo of age. Rams were given a bolus i.v. injection of GnRH (100 μg/2 mL; Cystorelin, Merial Limited, Duluth, GA). Jugular vein blood samples were collected at 20-min intervals from 1 h before until 4 h after the injection. To evaluate whether there was a long-lasting effect, blood samples were collected every 15 min from hour 24 to hour 25 post injection. Blood samples were centrifuged, serum collected, and frozen and stored at −20°C pending hormone analysis.

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