Simvastatin Reduces Fetal Testosterone Production and Permanently Alters Reproductive Tract Development in the Male Crl:CD(SD) Rat

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Androgen signaling by fetal Leydig cells is critical in the proper development of the male reproductive tract. As cholesterol is a precursor for hormone biosynthesis, inhibition of the cholesterol pathway during sex differentiation may reduce testosterone (T). We hypothesized that simvastatin (SMV), a cholesterol-lowering drug, would reduce fetal T, ultimately resulting in reproductive tract malformations in the male rat. In a prenatal assessment study, dams were given 0, 15.6, 31.25, or 62.5 mg SMV/kg/day via oral gavage from gestational day (GD) 14-18, which includes the critical period of sex differentiation in the rat. Fetal testicular T production and plasma lipid concentrations were measured at GD 18. In a postnatal assessment study, dams received the same doses of SMV from GD 8-18 (covering organogenesis and sex differentiation) or 62.5 mg SMV/kg/day from GD 14-18. Anogenital distance (AGD) and nipple retention were measured on postnatal day (PND) 2 and 13, respectively, and onset of puberty (measured by preputial separation, PPS) was monitored from PND 37 until complete. At necropsy, F1 adult males were examined for reproductive tract malformations. SMV exposure resulted in decreased fetal lipids and T production, with T levels reduced to 76.0 ± 3.9% and 62.8 ± 3.9% of control in the 31.25 and 62.5 groups, respectively ($p < 0.001$ vs control for each). In the postnatal assessment, there was a 92% mortality rate in the 62.5 (GD 8-18) group at birth. F1 males exposed to 31.25 mg SMV/kg/day had decreased AGD, delayed puberty (onset of PPS), and a 14.3% incidence ($p < 0.05$ vs control) of testicular malformations. In the 62.5 (GD 14-18) group, F1 males had decreased androgen-dependent tissue weights (seminal vesicle and LABC, $p < 0.05$ vs controls) and retained nipples. Together, these studies suggest that *in utero* exposure to SMV reduces fetal T production and permanently alters reproductive tract development in the male rat. *Abstract does not reflect U.S. EPA policy.*