Title: **Suppressing CXCL12-CXCR4 chemokine axis during implantation in sheep results in shorter fetal limbs and altered expression of glucose and amino acid transporters in fetal tissues at midgestation.**

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Placental insufficiency is a root cause of preeclampsia, fetal growth restriction, and fetal morbidity and mortality. The chemokine, CXCL12 and its receptor CXCR4 are implicated in pregnancy complications including miscarriage and preeclampsia but precise roles of this axis during placentation are unclear, especially at the fetal-maternal interface. Using a sheep model, we previously demonstrated suppressing CXCL12-CXCR4 signaling with a pharmalogical inhibitor (AMD3100, 1X dose) at the fetal-maternal interface during implantation reduces trophoblast invasion, disrupts uterine remodeling, and diminishes placental vascularization by d20 of gestation. At midgestation, these dams also exhibit placental insufficiency. In the current study a more in depth investigation into fetal growth and development was conducted concurrent with investigating impacts to fetus with increasing AMD3100 concentrations delivered. We hypothesized greater amounts of AMD3100 (1.5X and 3X doses) during implantation would cause dose-response negative impacts to fetal growth and development at midgestation. On d12 post-breeding, osmotic pumps were surgically installed in ewes to deliver two different amounts (1.5X or 3X) of AMD3100 or saline (control) into uterine lumen ipsilateral to corpus luteum for 14 days. On d90 fetuses were collected, weighed and growth measurements for fetal body, brain, liver, and heart weight, along with crown-rump length, thoracic circumference, and fore- and rear-limb lengths recorded. Fetal pancreas, small intestine, liver, and muscle were harvested, snap frozen in liquid nitrogen and stored at -80°C. Expression of mRNA for select glucose and amino acid transporters were analyzed using qPCR. The objectives were to determine if suppressing CXCL12-CXCR4 actions with varying doses of inhibitor during implantation impacts fetal growth/development and/or expression of glucose and amino acid transporters in select fetal tissues. Fetal body, brain, and liver weights did not differ between control and AMD3100 treatments. Crown-rump length and thoracic circumference was also similar. However, both fore and rear limb lengths were shorter ($P<0.05$) in fetuses from all AMD3100-treated ewes compared to control regardless of sex. In fetal liver, females had greater *GLUT1* and *SNAT4* expression with 1.5X AMD3100 compared to male and female controls. Conversely, males exposed to 1.5X AMD3100 displayed greater *SNAT1* and *CAT1* expression than control males or females. In muscle, *GLUT1* expression was suppressed by AMD3100 treatments in male and female fetuses. Control males expressed more *SNAT1*, *SNAT2*, and *SNAT4* than females but when exposed to AMD3100 treatments, males displayed decreased transcripts. Control females had greater *LAT1* expression than males however both sexes expressed less *LAT1* with 3X AMD3100. Regardless of sex, *LAT2* expression decreased with AMD3100 treatments while less *CAT1* was observed with 3X AMD3100 compared to control. In fetal pancreas regardless of sex, *SNAT2* expression decreased with 3X AMD3100 compared to control. In small intestine, *GLUT3* expression was less with 1.5X AMD3100 and less *SNAT1*, *SNAT2*, and SNAT*4* with 1.5X and 3X AMD3100 compared to control regardless of sex. Conversely, greater *LAT2* and *CAT1* expression occurred with 3X AMD3100 compared to control. Shorter limb lengths and altered expression of glucose and amino acid transporters in fetal tissues may indicate glucose and amino acid sparing mechanisms to ensure fetal survival and growth of brain and liver. Our model may prove useful to study pathogenesis of pregnancy disorders like preeclampsia and the corresponding impacts to the developing fetus. Research supported by National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH). Grant number 1SC1GM139712-01.