OBJECTIVE: To evaluate the effects of intra-amniotic (IA) and fetal injections of a single ultra-high dose of betamethasone (BM) 48 h before preterm delivery on neonatal pulmonary function, using an experimental goat model. STUDY DESIGN: Eighteen date-mated singleton pregnant Hair goats were randomized into four groups. At gestational day 118 (alveolar phase, term 150-155 days) after obtaining a sample of amniotic fluid, fetuses in group 1 (n=5) received 8 mg/kg IA BM, and in group 2 (n=5) 4 mg/kg fetal IM BM. In group 3 (n=4) (0.3mg/kg/day) maternal BM was administered at day 118 and 119 with a 24h interval; control fetuses (n=4) received 1 mL/kg of IA saline at day 118. At gestational day 120, after obtaining second sample of amniotic fluids 18 kids were delivered by preterm cesarean section, entubated, weighed, and mechanically ventilated for 15 min. Arterial blood gas samples and deflation/inflation lung pressure-volume measurements were obtained. After sacrifice, lungs were removed, weighed, gross examined and processed for further histological and immunohistochemical (IHC) evaluations. On hematoxylin and eosin (HE) stained slides, presence and severity of lung emphysema was evaluated; slides stained for surfactant proteins, and caspases were used for semi-quantitative evaluation of lung maturation. Kruskal-Wallis, Mann-Whitney, Wilcoxon signed rank, and chi-square tests were used for comparisons. RESULTS: IA BM was associated with increased number of stillbirths (60% vs. 0% in control) (p=0.06) and emphysematous changes. Bodyweight-adjusted pressure-volume measurements were improved after maternal, but not IA or fetal, BM (p=0.06). Following mechanical ventilation, arterial blood gas parameters did not significantly alter across maternal and fetal administrations. However, pH was significantly lower (p<0.05) and carbon dioxide partial pressure was higher (p<0.05) in the control group, indicating hypercapnic acidemia in non-treated pregnancies. None of the treatments induced measurable alterations in amniotic fluid lecithin/sphingomyelin (L/S) values. IA and fetal routes were associated with decreased surfactant protein expressions and increased apoptotic activity in alveolar and bronchio-alveolar epithelial cells. CONCLUSION: Ultra-high dose IA and fetal IM BM is not superior to the standard dose and maternal way of administration in our experimental design.