Antenatal sildenafil citrate rescues pulmonary vascular abnormalities in the rabbit model of congenital diaphragmatic hernia

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Objective
To evaluate the pulmonary vascular effects of sildenafil citrate (SC) in fetal rabbits with congenital diaphragmatic hernia (CDH).

Methods
27 fetuses from 12 time-mated does underwent surgical creation of CDH at d23 (term=31d); unoperated fetuses served as controls. The does were randomized to receive either placebo or SC 10 mg/Kg/day till sacrifice at term. Primary outcome measure was fetal ipsilateral pulmonary vascular morphometry and branching as measured by ex-vivo µCT of barium gelatin vascular casts (Figure). Secondary fetal measures were fetal loss rate, birth and lung weight. Maternal outcome measures were weight change, heart rate, behavior changes. Fetal and maternal SC plasma levels were measured by high performance liquid chromatography with spectrometric detection. Vascular indexes were compared (ANOVA) in the following groups: CDH+placebo, CTR+placebo, CDH+SC and CTR+SC.

Results
23 CDH fetuses and 23 controls were harvested. Fetal SC plasmatic concentration was above the minimal therapeutic level for at least 22 hours per day, without obvious maternal side effects. Peripheric (<60µm) pulmonary vessels of SC exposed CDH-fetuses had a medial and adventitial thickness in the normal range. 3D reconstruction and vascular quantification of µCT-scans showed that SC exposed CDH-fetuses had a normal total lung vessel volume, and a normal percentage of vessels of 5th generation or higher. CDH fetuses had significantly less 5th generation vessels and increased wall thickness.

Conclusion
In a larger animal model for CDH-induced pulmonary hypoplasia, antenatal SC rescues vascular morphology, branching and architecture. This is in line with what was observed in nitrofen-rats and paves the way for an antenatal medical strategy to prevent pulmonary hypertension in CDH.