



Antenatal Betamethasone Preserves Lung Structure and Function and Prevents Pulmonary Hypertension in Chorioamnionitis-Induced Bronchopulmonary Dysplasia

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Background

- **Bronchopulmonary dysplasia (BPD)**, the chronic lung disease of preterm birth, is characterized by arrested lung development, abnormal lung function, and increased risk for pulmonary hypertension (PH).
- **Antenatal steroids** improve many complications of prematurity, however, their role in attenuating BPD when administered in the setting of imminent preterm delivery has not yet been identified.
- Clinical studies have shown **strong associations of antenatal stress from chorioamnionitis (CA) with risk for BPD.**
- Administering **endotoxin (ETX)** into the amniotic space to mimic CA impairs infant lung growth and causes pulmonary hypertension (PH).
- **However, whether antenatal glucocorticoids reduce BPD and prevent PH in the setting of antenatal inflammation is uncertain.**

Hypothesis

We hypothesize that antenatal betamethasone (BETA) administration will help preserve lung growth and function and reduce PH in a rat model of CA-induced BPD.

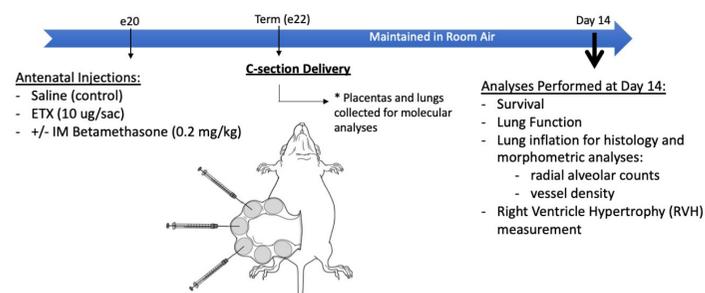
Study Questions

- 1) Does maternal administration of antenatal betamethasone improve lung structure and function in rat pups in a CA-induced model of BPD?
- 1) Does maternal administration of antenatal betamethasone prevent right ventricular hypertrophy (RVH) in rat pups in a CA-induced model of BPD?

Methods

- All animal procedures and protocols approved by the Animal Care and Use Committee at the University of Colorado Health Sciences Center.
- Timed pregnant Sprague-Dawley rats were used in our studies.

Methods: Experimental Model of Chorioamnionitis



Methods:

- Intra-amniotic endotoxin (ETX; 10 µg/sac) or saline (CTL; 50ul/sac) was administered to rat pups via laparotomy of pregnant dams at embryonic day 20 (E20; term, 22 days).
- Betamethasone (BETA; 0.2mg/kg) was administered to dams at E20.
- Pups were delivered by C-section at E22.
- Four subgroups were identified: saline (CTL), ETX, BETA, and ETX+BETA.
- Functional and morphometric analyses were performed at DOL14.

Day 14 Endpoint Analysis:

Lung function:

- Lung function was determined in 14-day-old anesthetized rats by using the flexiVent system (flexiVent; SCIREQ), which measures total respiratory system resistance and compliance according to standard methods from the manufacturer

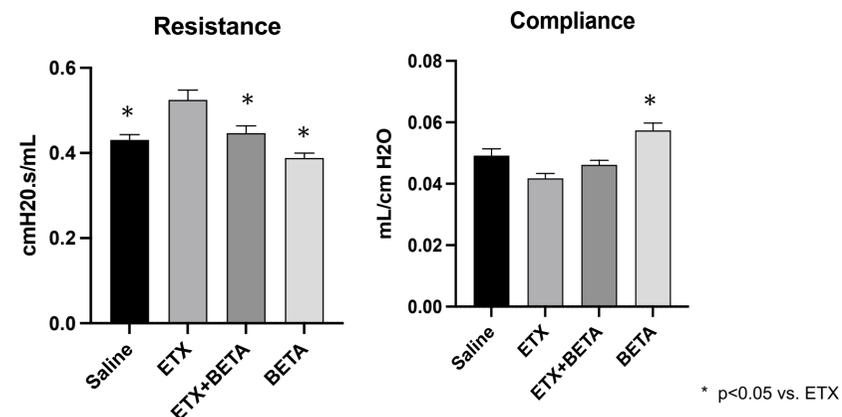
Radial Alveolar Counts:

- Radial alveolar counts (RAC) performed to determine distal lung structure via immunohistochemistry (IHC) staining with von Willebrand Factor immunostaining of endothelial cells used to identify pulmonary vessels for determination of vessel density

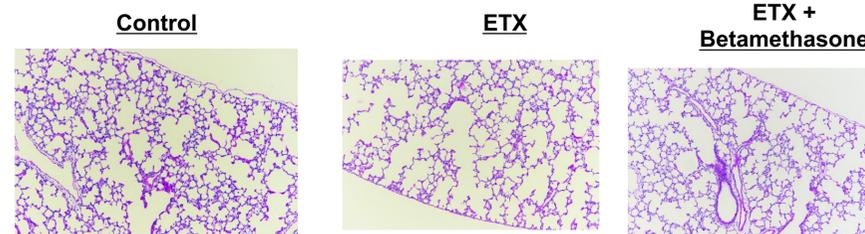
- **Assessment of RVH:** RVH was used as a marker for PH, as assessed via Fulton's Index: $RVH = RV / (LV + S)$ (RV= right ventricle weight; LV+S = left ventricle plus septal weight).

Results

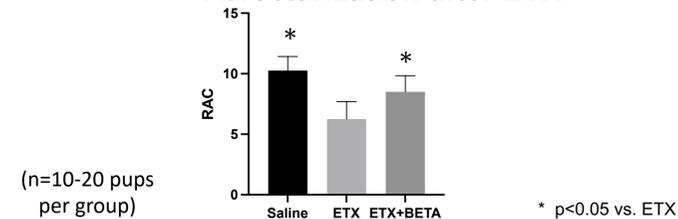
Antenatal Betamethasone Preserves Lung Function in Infant Rats After ETX



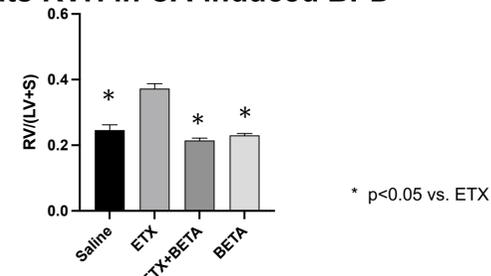
Antenatal Betamethasone Improves Distal Lung Growth and Structure after ETX



Antenatal Betamethasone Improves Alveolarization after ETX



Antenatal Betamethasone Prevents RVH in CA-induced BPD



Summary

- In comparison with controls, intra-amniotic ETX impaired lung growth, increased lung resistance, reduced compliance, and increased RVH at DOL14.
- Maternal BETA treatment of ETX-exposed fetal rats preserved distal lung structure and function and prevented RVH in infant rats:
 - reduced total lung resistance by 15.3% (p<0.05)
 - improved compliance by 9.5% (p<0.05)
 - preserved lung complexity as measured by alveolar growth as determined by radial alveolar counts (RAC; (p<0.05)
 - increased vessel density and improved RVH by 42.3% (p<0.05).

Conclusion

- **Antenatal betamethasone administration preserves lung structure, improves lung function, and prevents RVH in this rat model of CA-induced BPD.**

Speculation

- **We speculate that in the subgroup of pregnancies at risk for premature birth that are complicated by CA, antenatal steroids can reduce the risk for BPD.**