Maternal intravenous granulocyte-colony stimulating factor and intra-amniotic high-dose endotoxin for the experimental caprine model of chorioamnionitis

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Introduction

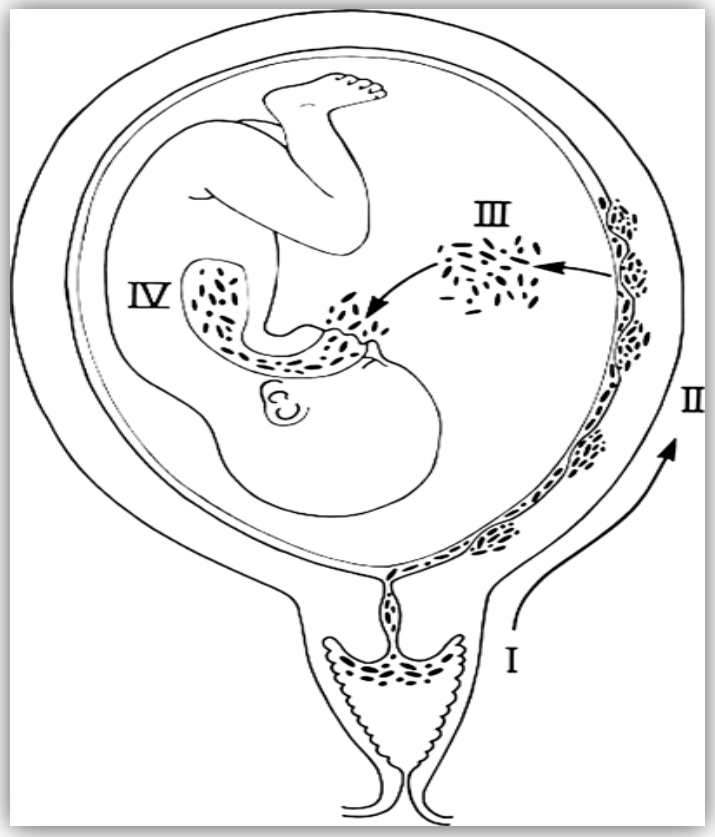
Intrauterine infection/inflammation has been identified as the most common cause of preterm delivery and neonatal complications such as brain injury and cerebral palsy.

http://www.marchofdimes.com

http://www.sercev.org.tr/

FIRS

Fetal inflammatory response syndrome



Romero R, J Nutr, 2003

The preterm goat model

- Goat: Commonly bred in the Lakes District, Turkey
- Suitable model to induce fetal lung and brain injury
- Fetal trx: Technically difficult in smaller animals but feasible in pregnant sheep and goat
- Convenient models for evaluating novel fetal trx modalities against FIRS.

Animal models for FIRS

- Premature goat and sheep models to induce fetal inflammatory response syndrome include administration of relatively low doses (10 mg) of endotoxin into the amniotic cavity.
- However, success rates have been inconsistent.

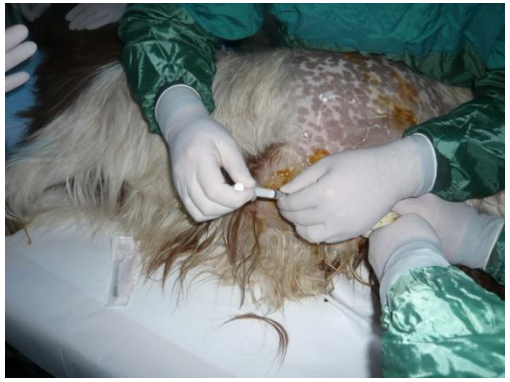
Objective

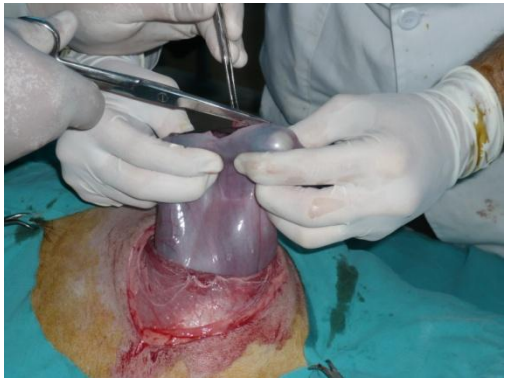
Here, we define our experience with daily intravenous (i.v.) granulocyte-colony stimulating factor (G-CSF) for 5 days followed by a single-dose of 20 mg intra-amniotic endotoxin to induce necrotizing funisitis/chorioamnionitis in the preterm fetal goat.

Methods (1)

- As part of the preliminary study of an experimental research project, pregnant goats (n=4) were given 50 µg/day (solubilized in 2 mL normal saline) G-CSF into the carotid vein as a bolus injection at gestational days 110-115 (term, 150 days) for 5 consecutive days.
- At gestational day 115, 20 mg of endotoxin (E. Coli O55:B5) was administered into the amnion under ultrasound guidance.

1. D110-115
   - G-CSF
2. D115
   - Endotoxin
3. D120
   C/S





D120 (goat) = 32+0/7 w (human)

Methods (2)

- Controls (n=4) received 2 mL of normal saline i.v. for 5 days and intra-amniotic saline infusion.
- Following preterm delivery at day 120 by cs, umbilical cords and membranes were harvested; histopathological examinations were performed.

Results: Macroscopic findings

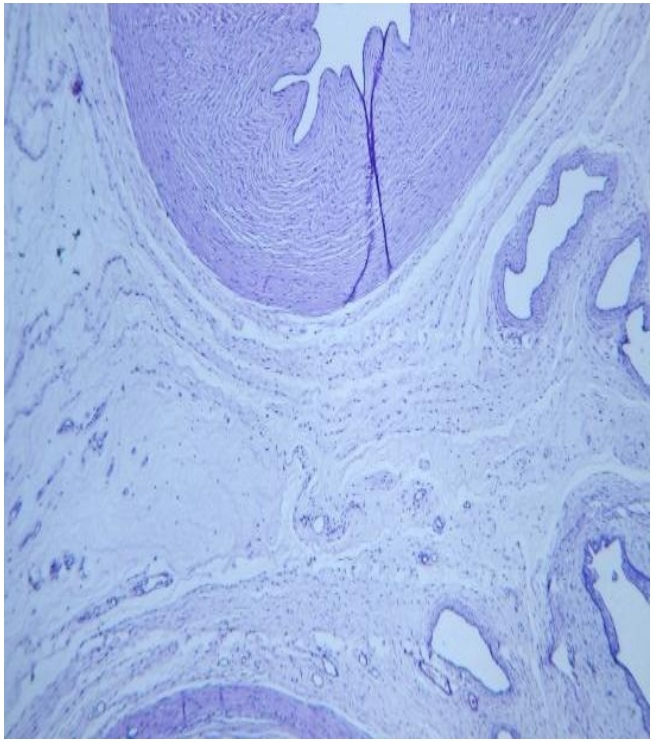
Umbilical cords of control animals (group 1) were macroscopically normal, whereas hemorrhage and edema were present in model animals (group 2)

Results: Cord pathology

- G-CSF and endotoxin-induced model was associated with widespread inflammation characterized by funisitis and vasculitis including vessels and Wharton jelly.
- Vascular thrombotic foci were observed in some vessels.
- Infiltrations were present in fetal membranes.

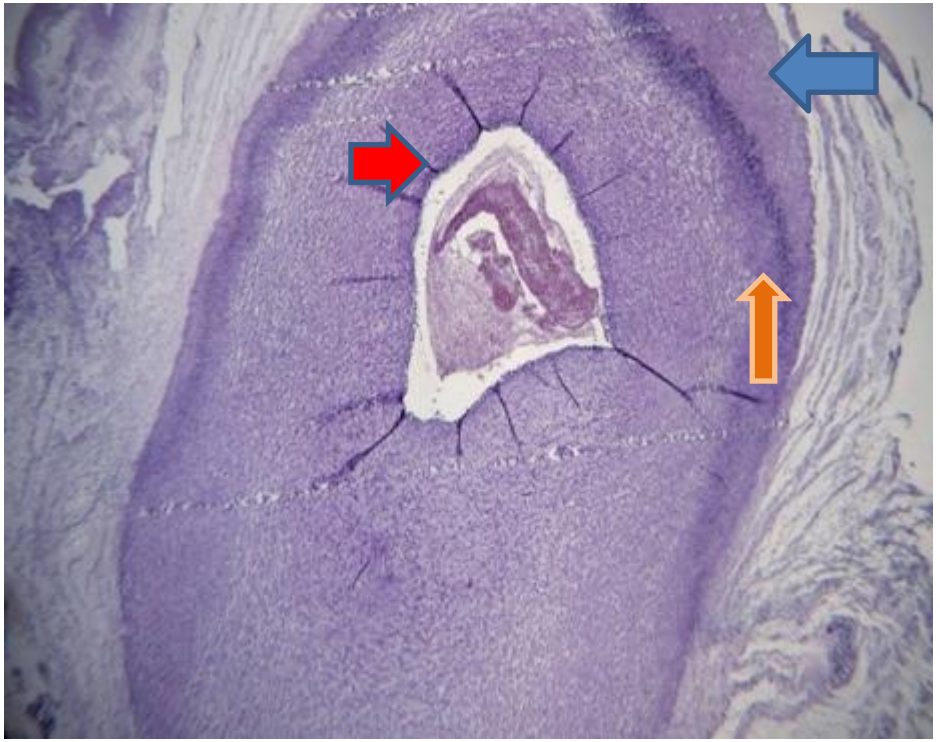
Umbilical cord findings

Group I



Control

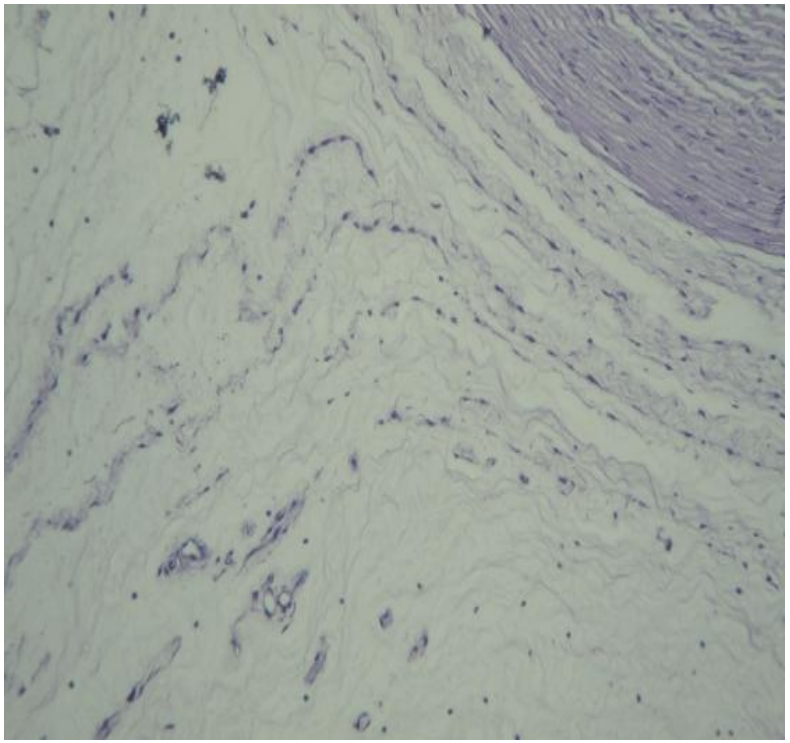
Group II



Model group: necrosis (blue arrow); inflammatory reaction (orange arrow) and thrombosis (red arrow)

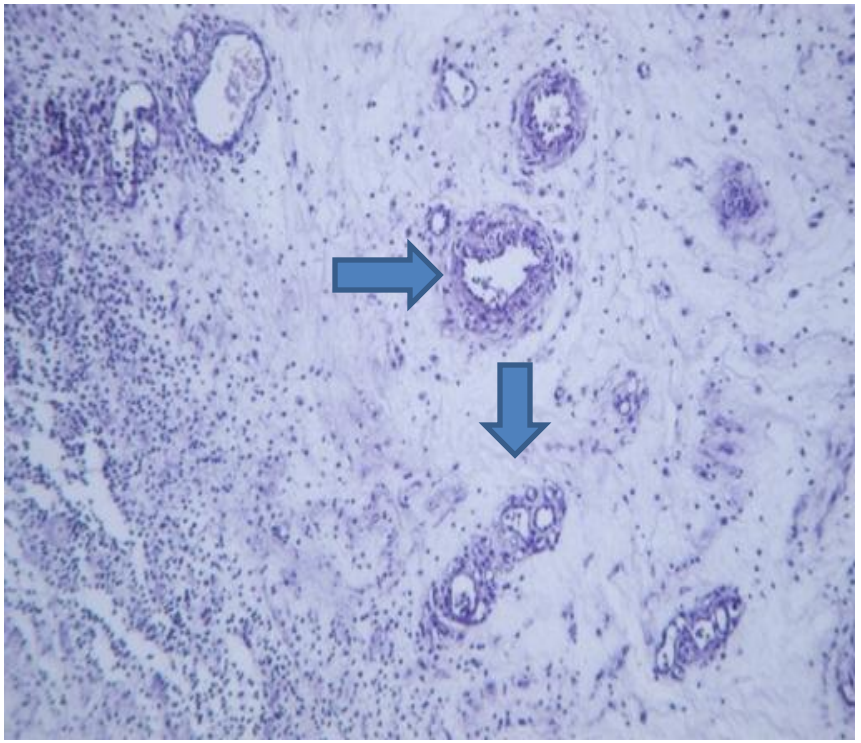
Umbilical cord findings

Group I



Control

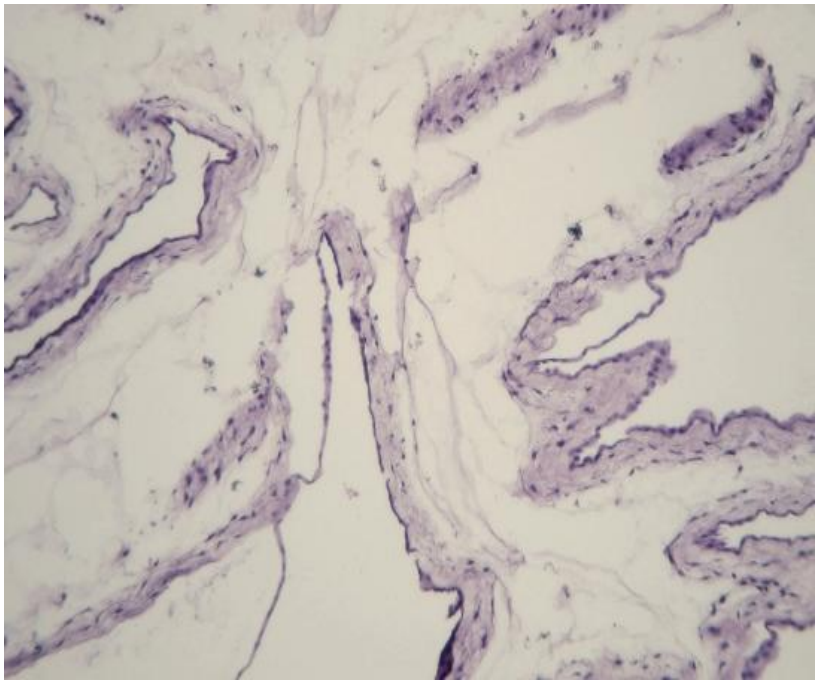
Group II



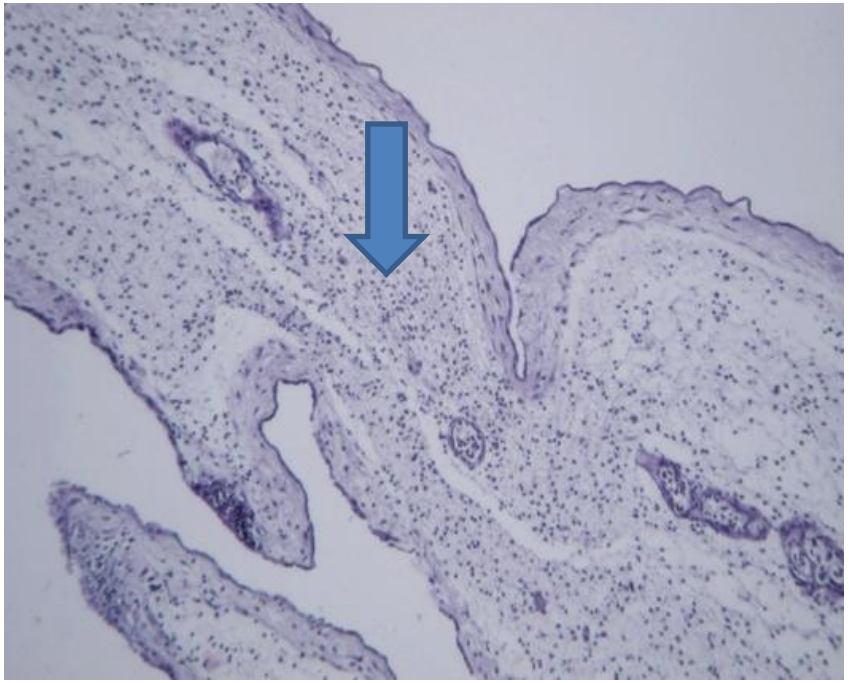
Vasculitis (arrows) in the model group

Fetal membranes

Group I



Group II



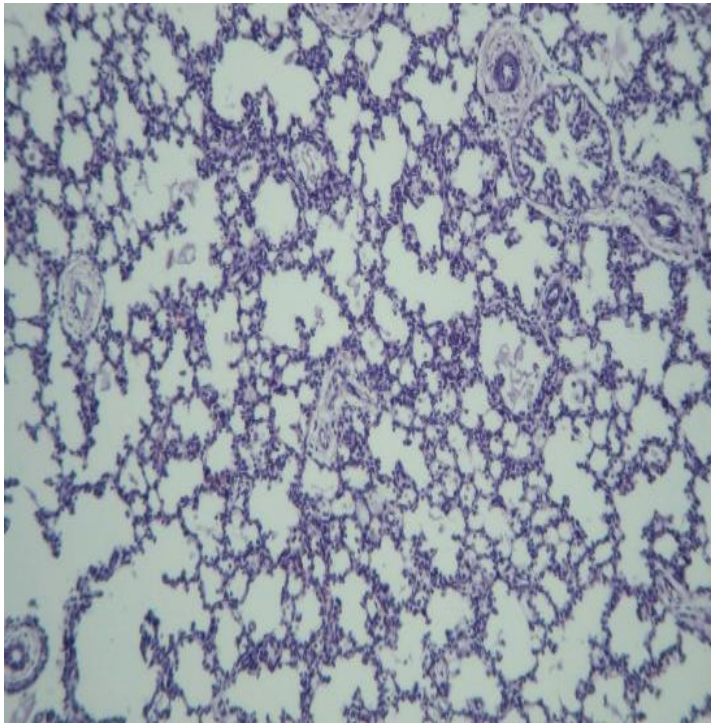
Normal (right) and inflamed (left) fetal membranes (blue arrow)

Fetal lungs

- Numerous macrophages and neutrophil infiltrations in group 2
- Alveolar septal walls were edematous and thick secondary to infiltrations
- Controls: Thin and normal septal tissues

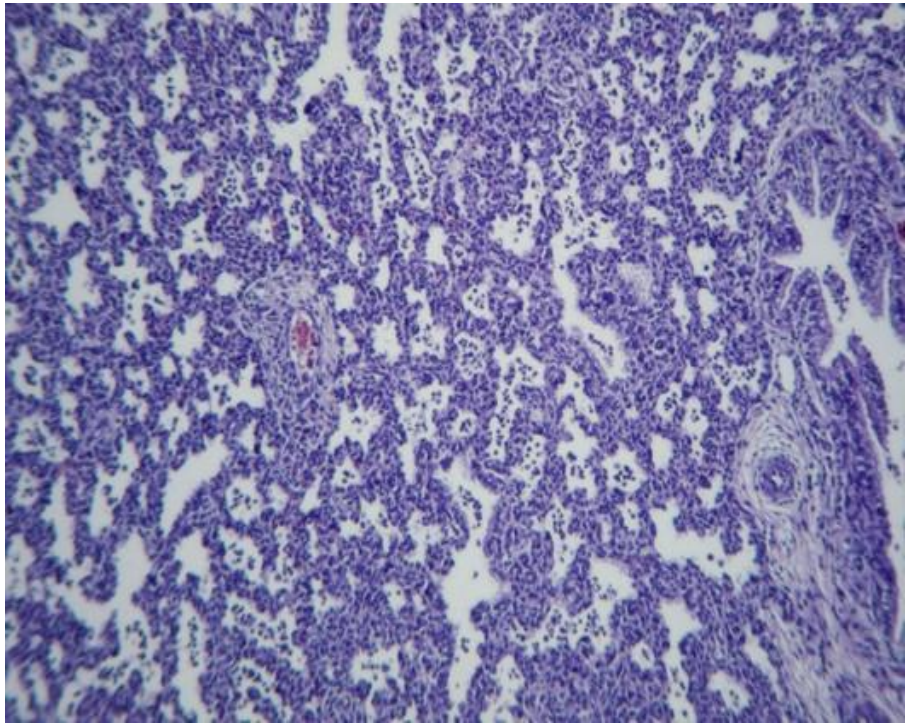
Fetal lungs

Group I (control)



Normal lungs

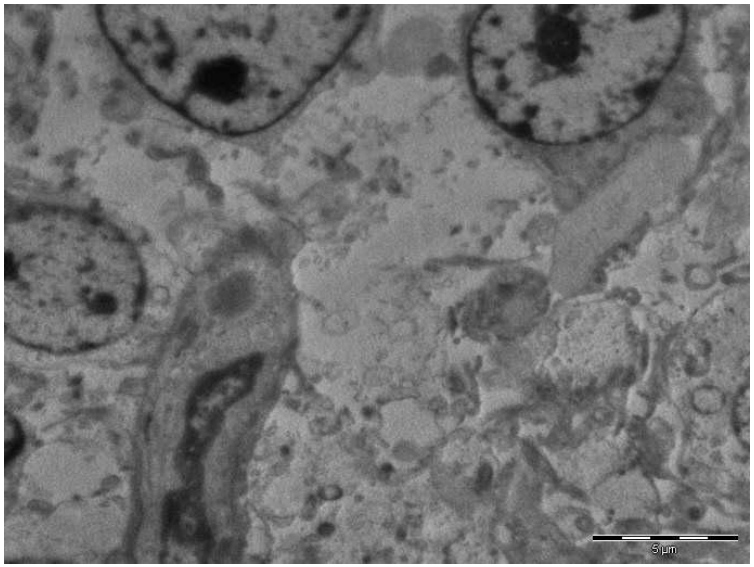
Group II (model)



Thick septal walls and infiltrations

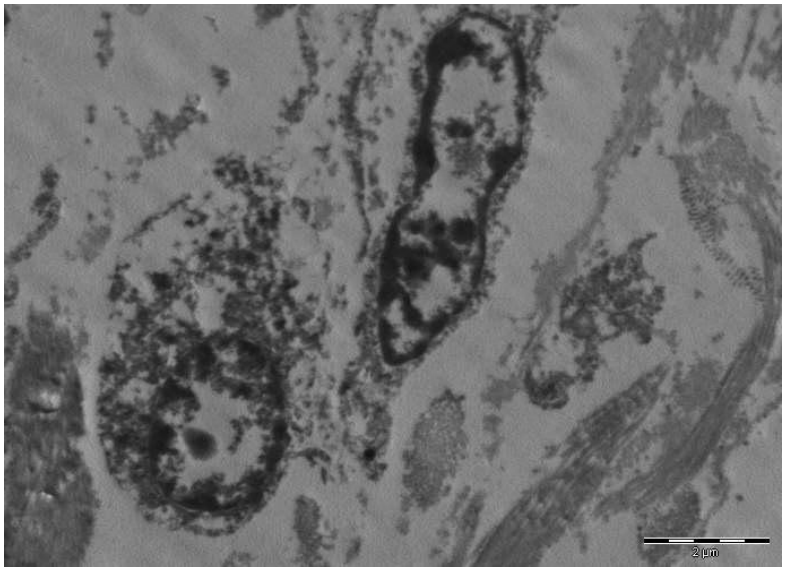
Fetal brain (e-microscopy)

Group I (control)



Normal brain: Mag x5000

Group II (model)



Fetal brain injury: Mag x12.000 TEM, chromatin condensation, membrane damage and tissue lysis

Conclusion

Maternal i.v. G-CSF for 5 days followed by 20 mg of intra-amniotic endotoxin is a feasible animal model to aggravate intrauterine inflammation and fetal lung/brain injury in the premature fetal goat.