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

Mekin Sezik¹, Özlem Özmen², Mehmet Halığür², Seyit Ali Köse¹, Afşin Köker³, Ahmet Aydoğan²

¹Süleyman Demirel University, School of Medicine, Department of Obstetrics and Gynecology, Isparta, Turkey; ²Mehmet Akif Ersoy University School of Veterinary Medicine, Department of Pathology, Burdur, Turkey; ³Mehmet Akif Ersoy University School of Veterinary Medicine, Department of Obstetrics and Gynecology, Burdur, Turkey

2 May 2014 - Antalya
Acknowledgment

Supported by funds from the Scientific and Technological Research Council of Turkey (research project no, 111S424)

Financial conflict of interest: None
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.
FIRS
Fetal inflammatory response syndrome

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.