Column E Explanation

1. Registration number.

47-R-0004

2. Number of animals used in this study.

9 Ewes

3. Species of animals used in this study.

Sheep (Ovis aries)

4. Explain the procedure producing pain and/or distress. (Procedure & animal experience)

Procedure: Pregnant ewes are administered bacterial lipopolysaccharide (LPS) endotoxin, (a cellular component extracted from E. coli cells) in late gestation to induce moderate systemic inflammation. LPS has been widely used in sheep and other research animals to study systemic inflammation because a.) it is generally safer for researchers and animals than live-bacteria injections, B.) it results in a typical and well-characterized animal experience in most cases, and c.) the effects of LPS on immune stimulation can generally be quickly reversed by administration of dexamethasone.

Animal Experience: The LPS treatment is intended to reflect a mild to moderate systemic infection or illness in the pregnant female (i.e. flu-like illness). Animal experiences are largely consistent and are characterized by mild to moderate clinical and physiological symptoms consistent with an immune response to systemic infection.

5. Explain why anesthetics, analgesics, tranquillizers could not be used.

Pregnant women are typically discouraged from using non-steroidal anti-inflammatory drugs (NSAIDs) to treat fever and inflammation, as the effects on the fetus are not well understood. However, the effects of fever/inflammation proper on placental function and fetal development are similarly unclear. Pregnant sheep are a commonly-used animal model for biomedical research due to key similarities between the human and ovine fetus. Thus, the objective of this study is to better understand how moderate inflammation during late gestation affects placental function and fetal development in the well-characterized pregnant ewe model, and whether concurrent NSAID treatment lessens or worsens the impact on the placenta and fetus. Untreated systemic inflammation in these animals reflects a common but under-studied human medical condition that appears to adversely impact perinatal and early-life health of the offspring. Moreover, treatment of the clinical symptoms of inflammation with NSAIDs (most common anti-inflammation/fever reducer used in non-pregnant humans and animals) will comprise a treatment group that will then be compared to the untreated group. Animals are closely monitored under the direction of the attending veterinarians, and our previous experience with this technique combined with literature reviews has allowed us to understand the ewe's normal physiological responses to LPS and to intervene when appropriate.

6. Federal regulations that require this procedure.

None

Column E Explanation

1. Registration number.

47-R-0004

2. Number of animals used in this study.

8 Ewes

3. Species of animals used in this study.

Sheep (Ovis aries)

4. Explain the procedure producing pain and/or distress. (Procedure & animal experience)

Procedure: IUGR lambs are produced by inducing placental insufficiency (PI) via maternal hyperthermia. Ewes are maintained in individual pens in our specially designed Environmental Chamber in conditions of 40°C for 12 h and 35°C for 12 h with a relative humidity of 30-40% beginning at d40 of gestation and ending at d95. The core body temperature (CBT) of the ewes will be measured daily (controls=thermoneutral, 25°C). The Environmental Chamber is designed to produce intrauterine growth restricted (IUGR) fetuses by exposure of pregnant ewes to elevated ambient temperatures, which results in an elevated maternal core body temperature of 0.6-1.0°C. In the sheep model of PI-IUGR, pregnant ewes are exposed for the period of pregnancy corresponding to that of maximal placental development and growth, from 40 dGA until 95 dGA – a period of 55 days in treatment. At 100 dGA, the ewes will be transferred to a thermoneutral environment, where they will remain for the duration of the study.

Animal Experience: The hyperthermic treatment is intended to reflect a mild to moderate environmental stress in the pregnant female (i.e. summer months). Animal experiences are largely consistent and are characterized by mild to moderate clinical and physiological symptoms consistent with hyperthermia, including small increases in CBT, respiration, and peripheral blood flow.

5. Explain why anesthetics, analgesics, tranquillizers could not be used.

Heat stress conditions are typically difficult to mitigate in livestock and humans. The effects on placental function and fetal development are unclear. Pregnant sheep are a commonly-used animal model for biomedical research due to key similarities between the human and ovine fetus. Thus, the objective of this study is to better understand how heat stress during gestation affects placental function and fetal development in the well-characterized pregnant ewe model, and whether prenatal interventions and /or postnatal treatments lessen or worsen the impact. Unabated heat stress in these animals reflects a common but under-studied human medical condition that appears to adversely impact perinatal and early-life health of the offspring. Treatment of the clinical symptoms in offspring will comprise a treatment group that will then be compared to the untreated group. Animals are closely monitored under the direction of the attending veterinarians, and our previous experience with this technique combined with literature reviews has allowed us to understand the ewe's normal physiological responses and to intervene when appropriate.

6. Federal regulations that require this procedure.

None