Perinatal pharmacology in ruminant models

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The primary physiological concern of the newborn is simply to survive. This is achieved only by the onset of a vast air–blood interface for gas exchange, the separation of pulmonary and systemic circulations, the maintenance of body heat which supplies the energetic cost for moving, and the development of immune responsiveness.

Use of drugs during pregnancy may produce adverse effects on the neuroendocrine factors during fetal development, and on the potential for functional adjustments at birth. The intensity of pharmacological effects depends on the magnitude of their pharmacodynamic actions on the fetus, and the extent of fetal exposure to the drug administered to the mother.

The chronic pregnant ewe model has been widely used to study the disposition and elimination of drugs in the ovine maternal–fetal unit by serial determinations over time during the last weeks prior to birth. Relevant data are scant on the pharmacological effect of reversibly-acting drugs on fetal development and postnatal behaviour.

The objective of this chapter is to show the pregnant ewe model as a tool to stress the key points of fetal growth and functional adjustments at birth susceptible to be involved in expected drug effects. It may be a way to bridge the gap between specialized disciplines concerned with developmental physiology and pharmacology.

Fetal Growth and Birth Weight

A positive relationship between neonatal mortality, the major form of reproductive loss in ruminants, and birth weight below the breed norms, has been recognized for many years (Figure 1.1). The birth weight of lambs, unlike that of human infants, is very sensitive to the level of maternal nutrition and to heat stress in the last third of pregnancy. In both cases, the weight of cotyledons is reduced. Hence, the idea has arisen of the surgical removal of...
cotyledons prior to conception in order to reduce fetal growth. That the placenta may limit fetal growth, particularly near term, is supported by (1) the high degree of association of fetal and placental weight in sheep (4.5:0.5 kg with a correlation coefficient of 0.84 between animals at 146–149 days of gestational age), (2) the intrauterine growth retardation obtained by surgically reducing the number of caruncles prior to conception, and (3) the occurrence during the last weeks of pregnancy of infectious abortions as a result of placental insufficiency. Hypotrophy has also been obtained by uterine artery ligation or by introduction of emboli into the maternal cotyledonary circulation. The ovine uterine blood flow increases from 0.5 ml/min per g placenta at 80 days gestation to approximately 3 ml/min per g placenta near term. The estimated growth rate during the last 30 days of pregnancy is 70 g per day and 3.7 times faster after birth.

**Maternal nutrition**

The sensitivity of the fetus to maternal nutrition is linked to the supply of glucose to the utero-placental mass, which consumes two-thirds of the glucose and produces about 50% of the CO₂. Relative to weight, the placental glucose utilization rate is 35 times the maternal rate and 10 times the fetal glucose consumption rate, hence the strong influence of the size of placenta on birth weight (Figure 1.2). A decrease of fetal growth rate by 40% occurs within 3 days of severe maternal underfeeding during the last 60–70 days of pregnancy. Change in birth weight is negligible when ewes are fed again after 9–16 days of undernutrition. In contrast, refeeding after 21 days has reduced growth rate of the fetus, suggesting the occurrence of a factor limiting the utilization of substrates by the fetus.

Low fetal growth rate is paralleled at birth by physical weakness. Thyroid and thymus glands are particularly small, and the emergency reservoir of blood in the spleen, blood glucose, the size of the liver and hepatic energy reserves are reduced. Lower thermal insulation at birth is related to the ratio of surface area to mass, e.g. it is 0.12 m²/kg in a 1 kg lamb, and 0.07 m²/kg