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REVIEW | *Model Systems for the Study of Integrative Physiology: The Rebirth of Translational Biology*

Improving pregnancy outcomes in humans through studies in sheep

Janna L. Morrison,[1] Mary J. Berry,[2] Kimberley J. Botting,[3] Jack R. T. Darby,[1] Martin G. Frasch,[4] Kathryn L. Gatford,[5] Dino A. Giussani,[3] Clint L. Gray,[2] Richard Harding,[6] Emilio A. Herrera,[7] Matthew W. Kemp,[8] Mitchell C. Lock,[1] I. Caroline McMillen,[1] Timothy J. Moss,[9] Gabrielle C. Musk,[10] Mark H. Oliver,[11] Timothy R. H. Regnault,[12] Claire T. Roberts,[5] Jia Yin Soo,[1] and Ross L. Tellam[1]

[1]*Early Origins of Adult Health Research Group, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia;* [2]*Department of Paediatrics and Child Health, University of Otago, Wellington, New Zealand;* [3]*Department of Physiology, Development, and Neuroscience, University of Cambridge, Cambridge, United Kingdom;* [4]*Department of Obstetrics and Gynecology, University of Washington, Seattle, Washington;* [5]*Robinson Research Institute and Adelaide Medical School, University of Adelaide, Adelaide, South Australia, Australia;* [6]*Department of Anatomy and Developmental Biology, Monash University, Clayton, Victoria, Australia;* [7]*Pathophysiology Program, Biomedical Sciences Institute (ICBM), Faculty of Medicine, University of Chile, Santiago, Chile;* [8]*Division of Obstetrics and Gynecology, University of Western Australia, Perth, Western Australia, Australia;* [9]*The Ritchie Centre, Hudson Institute of Medical Research, Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia;* [10]*Animal Care Services, University of Western Australia, Perth, Western Australia, Australia;* [11]*Liggins Institute, University of Auckland, Auckland, New Zealand; and* [12]*Department of Obstetrics and Gynecology and Department of Physiology and Pharmacology, Western University, and Children's Health Research Institute, London, Ontario, Canada*

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animal models; fetus; mother; placenta; pregnancy; sheep

HUMAN PREGNANCY, FETAL DEVELOPMENT, AND UTILIZATION OF APPROPRIATE ANIMAL MODELS

Development and growth of the human fetus, sequestered within its mother, cannot be directly observed. Lack of easy access to the human fetus limits our understanding of normal and abnormal human fetal development. This limited understanding hampers development of strategies to improve human health both before and after birth. Measurement of human fetal physiology by fetal blood or tissue sampling is not part of contemporary clinical practice and, because of the risks associated with such sampling, is not feasible in healthy human pregnancies. However, earlier studies, when human fetal blood sampling was more routine, confirmed that blood gas and hormone responses to intrauterine growth restriction (IUGR) in sheep models of IUGR are similar to those in human IUGR fetuses (110–112). Additionally, in fetal sheep models, multiple longitudinal blood samples can be obtained throughout

Address for reprint requests and other correspondence: J. L. Morrison, Early Origins of Adult Health Research Group, School of Pharmacy and Medical Sciences, University of South Australia, GPO Box 2471, Adelaide, SA, Australia 5001 (e-mail: Janna.Morrison@unisa.edu.au).

gestation; in humans, umbilical vein blood sampling is usually restricted to a single time point (258). Noninvasive (e.g., cardiotocography) and minimally invasive (e.g., chorionic villus sampling) techniques to assess fetal physiology and development are largely limited to high-risk human pregnancies and used primarily to inform clinical care. These techniques do not provide a full understanding of (ab)normal fetal growth or physiological, endocrine, or metabolic development, which is critical to improve the health of babies, including those born too small (because of IUGR) or too soon (because of preterm birth). Even "normal" fetuses may be exposed to a range of maternal health issues (e.g., asthma, mental illness, maternal stress, and drug use) and complications of pregnancy (e.g., gestational diabetes mellitus) that may require medications that impact the developing fetus. Therefore, understanding immediate and long-term effects of fetal exposure to potential therapeutic interventions is critical to establish the safety and efficacy of medication before widespread clinical use.

Compromised development in response to a suboptimal perinatal environment poses considerable health and economic burdens that can last for a lifetime, and even into the next generation. Preterm (<37 wk of gestation) birth affects ~15 million infants globally per year (46) and accounts for 16% of mortality in children <5 yr old worldwide (457). In Australia and New Zealand, rates of preterm birth are 7–9% (46). Rates are higher in North America and throughout the developing world. IUGR affects 5–15% of babies in developed countries and a much higher percentage in developing countries (30–55% of infants born in South Central Asia, 15–25% in Africa, and 10–20% in Latin America) (6, 93, 137, 246, 392). The additional comorbidity of preterm birth affects ~38% of IUGR infants (247), thereby amplifying their risk of poor health in later life (328, 415). Although modern perinatal care allows the majority of preterm and IUGR infants to survive the newborn period (194), it is now clear that there is a latent health "cost" for their survival. Preterm infants have a greater lifetime risk of poor cardiometabolic health, neurodevelopmental impairment, and behavioral and/or psychiatric problems than individuals born after an uncomplicated pregnancy (340, 402). IUGR is associated with a 50% greater risk of cardiometabolic disease in adult life and is also linked to increased rates of diabetes, obesity, and other adverse health outcomes (25, 26, 120, 123).

Many pregnant women use medication throughout or during part of their pregnancy to treat preexisting or pregnancy-induced illness (2, 14, 138). Despite this common exposure of pregnant women (and their unborn children) to medication, because of sex bias (toward males) of medical research subjects, maternal and fetal effects of medications are often understudied (239). The likelihood that maternal medications, including antidepressants, psychotropics, and paracetamol, have adverse effects on development of the fetal brain and other organs is only now starting to be appreciated (165, 172). In addition, many over-the-counter dietary supplements are not subject to the same regulatory procedures as prescription medications and are perceived as "natural" or "healthy" by consumers (336). The doses and timing of maternal supplement or pharmacological medication use can have a critical impact on offspring health. For instance, periconceptional folic acid supplementation reduces rates of neural tube defects, which led to international guidelines recommending its use and widespread food fortification (154). However, high maternal folate supplementation in late pregnancy is associated with increased risk of allergy in children (161). Further research is urgently needed to avoid unanticipated consequences that may emerge before or after birth and ensure either no harm or a net benefit to mother and baby.

Experimental studies that are relevant to human pregnancy rely on appropriate animal models. Consideration of the strengths and weaknesses of any animal model of human disease is fundamental to effective and meaningful translation of preclinical research to the clinic. Sheep have been used to study the normal and abnormal development of the fetus for almost a century. The pioneering research of Barcroft, who likened the low O_2 concentration of the fetal environment to living at the top of Mt. Everest (22), was performed in anesthetized ewes (23, 24). Subsequently, Liggins used pregnant sheep to conduct research on the control of parturition and antenatal corticosteroid therapy before preterm birth (265) followed by clinical trials in partnership with the pediatrician Ross Howie (267) that revolutionized perinatal medicine. In addition, the work of Dawes et al. using a sheep model, which led to understanding of fundamental fetal-maternal physiology, still forms the basis of clinical teaching in obstetrics, neonatology, and maternal-fetal medicine (88). More recently, research using pregnant sheep has allowed a deeper understanding of how suboptimal embryonic or fetal environments contribute to the emergence of poor health in later life (295). These advances are only the beginning, with many more in our future, as evidenced by the recent development of a "biobag" and pumpless oxygenator to allow growth and development of the preterm lamb outside the womb for a month (359) and the possibilities for advances in clinical care that are presented by this first step (41).

Use of sheep as an animal model of human pregnancy has enabled scientists and clinicians to answer questions about the etiology and treatment of poor maternal, placental, and fetal health in the unanesthetized fetus since the 1970s. The utility of smaller animals for studies of early development and genetic contributions to development and disease has led, in some cases, to the replacement of the sheep as a model of human pregnancy. We believe that a multiplicity of appropriate experimental animal models is an asset for any scientific field. Researchers must be able to identify the most appropriate animal model for research that will inform and translate to fundamental advances in the care of pregnant women and their babies. In our experience and based on the clinical translation of past research, a number of fundamental physiological questions (22, 88, 265), including those requiring direct measures of fetal physiology, are best answered by studies in sheep models. Thus, the aim of this review is to document the contribution and benefits of sheep in studies of fetal development and pregnancy to better inform clinical practice in humans (Table 1).

EVIDENCE BASE FOR SELECTION OF SHEEP AS A MODEL OF HUMAN DEVELOPMENT

Fact 1: Physiological Information Derived Directly From Studies in Sheep Pregnancy Has Been Successfully Translated to Standard Clinical Practice in Human Perinatal Care

Critical advances in perinatal medicine, which have substantially reduced mortality and morbidity for countless infants throughout the world, are directly attributable to experimental research carried out in sheep. Comprehensive physiological research over several decades has provided a depth and breadth

Table 1. *Facts about use of sheep as an animal model for perinatal research*

Fact 1: Physiological information derived directly from studies in sheep pregnancy has been successfully translated to standard clinical practice in human perinatal care
Fact 2: Surgical instrumentation to study fetal development over long periods of time, as needed for translating outcomes to humans, is readily achievable in sheep
Fact 3: Each animal model of human development is costly; sheep models are a cost-effective way to understand perinatal well-being, as they permit multiple and longitudinal output measures from the same animal
Fact 4: Study of outcomes in reproductively intact animals of both sexes is possible in a research setting
Fact 5: Development of major organ and regulatory systems occurs before and around birth in sheep, as in humans, but after birth in rodents
Fact 6: 'Omic studies in sheep are a helpful tool in understanding complex gene-environment interactions
Fact 7: Epigenetic responses in sheep to an altered perinatal environment can be usefully explored across different time periods in development
Fact 8: CRISPR technologies open new windows of opportunity for genetic manipulation studies performed in sheep
Fact 9: Sheep can be used in neurodevelopmental studies owing to similarities between stages of brain development in sheep and humans
Fact 10: Many important placental physiological characteristics are shared between sheep and humans
Fact 11: Sheep are an important model of glucose metabolism during pregnancy and the programming effects of an adverse uterine environment on glucose metabolism in the offspring
Fact 12: Sheep are a good model to investigate causes and consequences of preterm birth

of knowledge from the preconception period through embryonic, fetal, and neonatal life and, finally, in offspring followed into adult life. These studies have enabled interrogation of normal and (mal)adaptive responses and developmental changes in healthy pregnancies and those in which clinically relevant pathological states have been imposed.

Antenatal corticosteroids for women at risk of preterm birth. The remarkable ability of corticosteroids to stimulate lung maturation, enabling viability after preterm birth, was first shown in sheep by Graham "Mont" Liggins. From his initial observations in a handful of preterm lambs, he progressed immediately to conduct the first human randomized controlled trial (RCT) in perinatal medicine, which was also among the first RCTs performed (264, 267). Meta-analysis of the results from this and dozens of subsequent trials shows clear life-saving benefit of maternal antenatal corticosteroid administration for preterm human infants (385). Today, the treatment is used in many countries as standard clinical practice and remains essentially unchanged from that devised by Liggins from his experiments in sheep >50 years ago.

Sheep continue to be used to refine and improve efficacy and safety of antenatal corticosteroid therapy. Attempts to augment the effectiveness of antenatal corticosteroids with other maturational agents have been as unsuccessful in sheep as they have been in humans (1, 79, 81, 82, 163, 201, 203, 206). When concerns were raised about potential effects of antenatal corticosteroids on fetal growth, brain development, and cardiovascular function in human infants, these effects were determined and verified using sheep, which allowed the underlying mechanisms to be understood (202, 332, 333). Subsequent experimental studies using sheep showed long-term effects of repeated antenatal corticosteroids on postnatal physiology (405, 406), with persistent effects on brain development (321). These studies provided the impetus for RCTs in humans (30, 78) and their follow-up from Liggins' initial RCT (293, 294). Antenatal corticosteroid therapy is an off-label use of agents approved for other medical indications. Studies in sheep continue to seek to identify more effective corticosteroid preparations (218, 219, 235) and routes of administration (320) to improve efficacy and safety. At the same time, RCTs (e.g., A*STEROID) continue with the same aim (80). As more data become available from sheep experiments and the results of ongoing clinical studies provide information about the effects of antenatal corticosteroids in contemporary clinical practice, integration of information from both sources will continue to benefit individuals born preterm.

The benefit of antenatal corticosteroid therapy in threatened preterm birth is unequivocal. However, there is a trend toward its use at, or near, full term to improve newborn respiratory function, especially after prelabor cesarean section. As fetal maturational state at late gestation is profoundly different from that preterm, excess systemic corticosteroid exposure late in gestation may lead to unanticipated adverse consequences. Studies in sheep have identified unfavorable long-term sex-specific effects of maternal corticosteroid treatment in near-term fetuses (42). Thus, follow-up studies of infants already exposed to antenatal corticosteroid therapy near term are required to fully understand the cost-to-benefit ratio of this approach.

Artificial reproductive technologies. Artificial mammalian reproduction strategies were first developed in sheep and cattle to facilitate selective breeding for the commercial improvement of livestock. Underpinning this technology development was the discovery in these animals of hormones playing pivotal roles in mammalian reproduction. This technology has rapidly been adapted to assist human reproductive success. Techniques such as superovulation, oocyte culturing, in vitro fertilization, and embryo maturation, transfer, and freezing originate from studies in sheep and cattle (52, 209, 253, 278, 305, 463, 464). The livestock industry similarly pioneered techniques for fertilization of oocytes using frozen semen and sexing of sperm (440).

Genetic mutations in sheep have also provided a more complete understanding of the roles of specific genes in human fertility. Genetic mutations in the sheep genes growth differentiation factor 9 (*GDF9*) and bone morphogenetic protein 15 (*BMP15*) were identified and found to impact twinning rates and fertility (140, 173). Soon after these discoveries, mutations in the orthologous human genes were shown to be associated with premature ovarian failure and spontaneous dizygotic twinning (95, 98, 304).

Somatic cell nuclear transfer technology (61) was used to produce the first cloned sheep in 1996 (Dolly, Scotland) and 2000 (Matilda, South Australia; http://www.abc.net.au/science/articles/2000/05/04/123089.htm). This technology highlighted the technical capability to reprogram somatic cells (mammary epithelial cells in the case of Dolly) and stimulated expansive research into stem cell applications for use in hu-

mans that have potential to treat a range of human diseases (71, 430).

Therapeutic hypothermia for asphyxiated newborns. Hypoxic-ischemic encephalopathy is one of the catastrophic consequences of intrapartum asphyxia and a leading cause of brain damage in full-term newborns (212). The prognosis for affected infants has traditionally been bleak, with high rates of mortality or severe neurological impairment in survivors. Therapeutic hypothermia, a reduction in core temperature (from 37°C to 33.5°C) following an asphyxial insult, has transformed the outlook for these infants and is recognized as the first targeted treatment to increase rates of disability-free survival. Whole body cooling is, therefore, now the international standard of care for affected human infants (424). The experimental research underpinning this innovative treatment was conducted in fetal sheep before translation to human clinical trials (152, 168, 169). Crucially, the instrumented fetal sheep model allows exposure of the fetal lamb to a variety of complex environmental or pharmacological stressors. As the lamb remains in utero, the mother in essence acts as a surrogate intensive care unit, supporting its physiological stability without the confounding effects of anesthesia or other clinical interventions that would be necessary to support postnatal life. This enables the pathophysiological effect of injury and its consequences, as well as the response to and efficacy of treatment, to be followed in detail over time.

Neonatal ventilation and exogenous surfactant. Beginning with Bargellardus's recommendation to midwives in 1472 that, for an infant that is "warm, not black," they should "blow into its mouth, if it has no respiration" (19), artificial respiration and resuscitation have gone hand-in-hand with neonatology. Refinements in neonatal respiratory support continue, with the aim of identifying the optimal means to resuscitate and support breathing in newborns. Mechanical ventilation (cyclic positive-pressure ventilation) to support respiration of preterm infants gained popularity in the early 1960s after publicity surrounding the death of preterm infant Patrick Bouvier Kennedy (son of Jacqueline and President John F. Kennedy) from hyaline membrane disease [now called respiratory distress syndrome (RDS)]. As the use of mechanical ventilators for preterm infants increased, it became evident that, inadvertently, excessive pressures and volumes delivered to the lungs of preterm infants could cause pneumothorax and contribute to more subtle injury, leading to chronic lung disease, or bronchopulmonary dysplasia (BPD).

Experiments using preterm lambs showed that mechanical ventilation with hyperoxic gas for an extended period could cause lung pathology characteristic of BPD (364). Other experiments in sheep showed that only a few high-volume breaths at birth could cause lasting impairments in respiratory function in preterm lambs (44). Because of such experiments, it is now recognized that mechanical ventilation of immature lungs initiates lung injury and inflammation (190) and that abnormal lung structural development is common when the developing lungs are removed from the fluid-filled intrauterine environment and forced to become the sole site of gas exchange.

In attempts to reduce lung injury in preterm babies who need respiratory support, alternative ventilation modalities have been trialed in sheep, in parallel with their use in human infants. Although able to provide sufficient respiratory support, these alternatives do not appear to protect against lung inflammation and BPD. Experimental studies of the use of positive end-expiratory pressures (PEEP) during mechanical ventilation (404), showing physiological benefit for preterm lambs, have informed the use of PEEP in neonatal intensive care units and delivery rooms. The use of initial sustained inflations during aeration of the lungs showed benefit for achieving effective ventilation and stabilizing the circulation at birth (427). Similarly, the use of lower levels of inhaled O_2 with PEEP, avoiding potentially harmful effects of hyperoxia, has been demonstrated to be effective in resuscitating neonatal lambs (371) and is now recommended for use in human preterm resuscitation (307).

The only ventilatory modality proven to reduce rates of BPD in human infants, apart from avoidance of prolonged use of hyperoxic gas, is the use of continuous positive airway pressure (CPAP) to support spontaneous breathing (414). After clinical evidence emerged showing the benefit of CPAP, studies in preterm lambs demonstrated that it protected against lung injury and inflammation (217). Refinement of the use of CPAP in lambs has reached the point at which a realistic preterm lamb model of CPAP can be used to mimic contemporary clinical management of preterm infants (217). Studies in preterm lambs showed that, for CPAP to provide effective support, a minimal level of pulmonary surfactant is required in the preterm lungs (190). Sheep were among the many animal species (including mice, rabbits, rats, and hamsters) used by Mary Ellen Avery and others in their pioneering studies of surfactant in newborns from the late 1950s onward (73). Those studies led to the development of exogenous surfactant to treat RDS in preterm infants, a therapy still in routine clinical practice.

Development of fetal surgical techniques. Significant congenital malformations, such as spina bifida and congenital diaphragmatic hernia (CDH), or vascular malformations, such as those seen in twin-twin transfusion syndrome, are uncommon, yet they carry a high burden of mortality and morbidity (290). Traditionally, the only therapeutic options consisted of supportive care in utero followed by expedited delivery for those at risk of imminent fetal demise and postnatal surgery. Interventional studies in fetal sheep revolutionized the outlook for affected babies (298). With the advent of open fetal, or fetoscopic, surgery for babies with spina bifida or CDH and development of noninvasive techniques for twin-twin transfusion syndrome, such as high-intensity focused ultrasound vascular disruption (399), mortality and morbidity rates have fallen (290). Ongoing refinement of surgical technique (357), exploration of new fields of intervention (113, 114), and development of biomaterials are driven by the ability to simulate and then correct such malformations in the sheep fetus. Advances in fetal surgery and the ability to provide extrauterine support that mimics intrauterine support may allow for correction of congenital heart defects earlier and recovery with a fetal, not postnatal, circulation.

Fact 2: Surgical Instrumentation to Study Fetal Development Over Long Periods of Time, as Needed for Translating Outcomes to Humans, is Readily Achievable in Sheep

Nonhuman primates are perceived as the "gold standard" animal model for translational studies of human development (108). This may be true for physiological processes during

development that are highly species-dependent, such as the mechanisms promoting parturition. In such cases, the contribution of nonhuman primate research is unquestionable (105, 296, 330, 362). However, the use of other species is merited to study generic physiological processes that are controlled by broadly similar mechanisms across multiple species for the following reasons.

First, access to primate species for use in biomedical research is limited due to ethical concerns of prolonged captivity, the requirement for, and cost implications of, specialized environmental enrichment and housing, zoonotic disease risk, and the extent to which human-experimental animal bonds may develop. Of course, all animal research carries an ethical cost that needs to be justified in terms of potential benefits, and researchers and animal caregivers also develop bonds with other large animals, including sheep, and, in particular, during long-term studies.

Second, highly invasive studies in nonhuman primates, such as those requiring fetal instrumentation, are not sustainable not only due to the financial expense, but also the high physiological cost to both the mother and fetus. For example, the risk of preterm delivery resulting from poor resistance to uterine invasive surgery in primates relative to other species is extremely high and, therefore, prohibitive. In situations where use of nonhuman primates is not appropriate or feasible, sheep have many advantages over most other species, including nonhuman primates, as an ideal experimental model for human clinical translational research. In work with animal models of physiological dysfunction before birth, similar temporal profiles of the development of various systems between species are essential to achieve translation to the human clinical situation. Unlike humans, rats and mice are altricial species, in which maturation of several organ systems, such as the brain and cardiovascular system, continues past birth and is not complete until well into postnatal life (390). Rodents, pigs, and guinea pigs give birth to litters, whereas humans and sheep generally carry singletons; thus, differences in maternal metabolic adaptations to pregnancy between litter- and singleton-bearing species also require consideration. In contrast, sheep and humans share similar prenatal patterns of precocial brain and cardiovascular development (390). Furthermore, some breeds of sheep, such as Welsh Mountain and Merino, give birth primarily to singleton lambs similar in weight to full-term human babies.

Third, the sheep is the only animal model that is sufficiently resilient and large to permit surgical instrumentation of the mother and fetus for in vivo recording of cardiovascular variables and electrical signals and to enable blood sampling for endocrine and metabolic measurements over long periods of time (57, 126, 311, 368; for reviews see Refs. 148 and 308). Although recording for several days has been reported in chronically instrumented maternal and fetal horses (83, 149, 342, 472), pigs (131, 175), guinea pigs (309, 435), goats (84), and llamas (109, 150, 151, 185, 275), recording over weeks to months has been possible only in sheep. Wireless technology has enabled continuous recording of cardiovascular and electrical signals from chronically instrumented maternal and fetal sheep (12, 49). For example, a telemetry device has been used to record renal sympathetic nerve activity for hours to days (12, 49, 50). Simultaneous recording of multiple blood pressure and blood flow signals from the mother and fetus in vivo in real time over months in free-moving sheep in controlled local environments can be achieved (12). Comparable approaches have not been developed in another species, but as telemetric technology improves, blood flow, as well as blood pressure, recordings may eventually be possible also in rodents. Bioethically, such refined technology enhances the physiological quality of the cardiovascular data and improves animal welfare, abiding by the 3Rs (replacement, reduction, refinement) principle (426) enshrined by the ethical review groups of many countries.

This range of technologies for continuous measurement of physiological parameters is possible because of the ability to perform surgery in the sheep fetus (Table 2). The size of the pregnant ewe also means that comprehensive physiological monitoring during anesthesia and in the postoperative period is possible (282). Ensuring that the physiological status of the ewe is within normal limits is important, especially during anesthesia, to maintain a healthy fetus. Monitoring the mother and fetuses to the same degree during surgery is impossible in rodent models. In sheep the cardiovascular and respiratory responses to anesthesia, pregnancy, and interventions can be assessed continuously and reliably by electrocardiography for heart rate and rhythm; pulse oximetry for oxyhemoglobin saturation, peripheral perfusion, and pulse rate; and capnography for adequacy of ventilation, blood pressure measurement, uterine blood flow, and cardiac output. Body temperature, blood gases, and acid-base status are also easy to monitor and

Table 2. *Experimental techniques possible during pregnancy in a range of species*

	Sheep	Pigs	Goats	Mice	Rats	Rabbits	Guinea Pigs	Primates
In vivo physiological measures								
Of the mother								
Invasively		✓	✓	✓	✓	✓	✓	✓
Noninvasively	✓	×	×	✓	✓	✓	✓	✓
Of the fetus								
Invasively	✓	✓	✓	×	×	×	×	✓
Noninvasively	✓	×	✓	✓	✓	✓	✓	✓
In vitro analysis of maternal and fetal tissues								
Gene and protein studies	✓	✓	×	✓	✓	✓	✓	✓
'Omic approaches used	✓	✓	×	✓	✓	✓	✓	✓
Immunohistochemistry	✓	✓	×	✓	✓	✓	✓	✓
Genetic manipulation or cloning before development of CRISPR	✓	✓	×	✓	✓	×	×	×
CRISPR	✓	✓	✓	✓	✓	✓	✓	✓
Primary culture of cells	✓	✓	×	✓	✓	✓	✓	✓

✓, Studies performed; ×, no studies identified.

manage in a pregnant ewe. The principles and practice of clinical anesthesia of humans can, therefore, be applied to sheep, and new approaches can be developed with involvement of veterinary anesthetists (68).

Furthermore, with use of noninvasive clinical techniques, such as assessment of cardiovascular function by fetal heart rate variability, Doppler ultrasound, and functional echocardiography, in parallel with chronic instrumentation during experimental physiological challenges, studies in the sheep fetus can improve the interpretation of clinical measures of fetal health in human obstetric practice (121, 221, 337, 351). Much of the current understanding about behavioral states and cardiovascular development in the human fetus has been validated in studies using sheep.

In addition, development of several models of IUGR in sheep is important, because each model mimics different aspects of this heterogeneous condition (for review see Refs. 158 and 308). IUGR can be induced in the sheep through maternal undernutrition (101), maternal exposure to hypobaric (12, 53) or isobaric (12, 53) hypoxia, uterine artery compression (47), umbilical cord occlusion (35), placental embolization (74, 280, 281), maternal overnutrition in adolescence (446), early-through-midgestation heat stress to disrupt placental development (34, 378, 389), ligation of a single umbilical artery (299, 300), high-altitude pregnancy (147, 184, 211, 279, 361), and surgical removal of placental attachment sites before mating (11, 143, 310, 386). These multiple approaches provide models of IUGR reflecting the most common causes in humans: poor placentation and restricted oxygenation and nutrition (308). These models result in IUGR with an onset in early or late gestation due to their chronic nature, rather than the acute nature of many rodent models (e.g., the last 2–6 days of gestation) (60, 343, 467). Extensive studies in IUGR sheep have provided direct proof that IUGR due to poor placentation impairs fetal and postnatal cardiometabolic health (74, 144, 448). Together with other studies, this research has increased awareness of the need for monitoring the health of humans who were born IUGR and their particular need for surveillance if they develop health challenges, such as obesity, hypertension, and coronary artery disease, to which they may be particularly susceptible.

Fact 3: Each Animal Model of Human Development Is Costly; Sheep Models Are a Cost-Effective Way to Understand Perinatal Well-Being, as They Permit Multiple and Longitudinal Output Measures From the Same Animal

All animal models are "expensive," but when a human model is not appropriate, animal models are an alternative. With a clear research question and sound methodology, animal studies have an invaluable role to play in the acquisition of evidence to support changes in clinical care or therapeutic interventions in humans and animals. In sheep, the ability to obtain multiple measures at different time points across gestation in the same set of animals is extremely valuable in studies assessing developmental programming. Serial collection of fetal physiological data can be carried out for weeks to months (12, 75, 186, 291, 314, 319) and related to tissue analyses from multiple organs. This longitudinal advantage of the sheep model is in contrast to smaller species, where one animal (or an entire litter) must be used at each time point and often for each measure. For example, it is possible to collect muscle biopsies over time to assess insulin-signaling responses (291) and circadian changes (438) in sheep, whereas similar studies in rodents require separate groups of animals for tissue collection at each time point (63, 437). Consequently, in small-animal models, many more animals must be used over a longer period of time, and, as a result, the real costs, including finances, time, and animal impact, are higher than one might expect on a relative basis. While nonhuman primates also allow for the collection of biopsies, the cost associated with nonhuman primate research is substantially greater than that associated with research on sheep because of the facilities required to perform studies that are consistent with the ethical guidelines (96, 164, 237, 238). Furthermore, the trend toward understanding complex traits through integration of multiple 'omics data sets with higher-order phenotypic data typically requires multiple samples from tissue or blood. This type of sampling strategy is much more practical in larger animals, such as sheep, than smaller animals. This issue is accentuated if multiple technical replicates, in addition to biological replicates, are used in the 'omics analyses.

Fact 4: Study of Outcomes in Reproductively Intact Animals of Both Sexes Is Possible in a Research Setting

Animal husbandry practices used in commercial livestock production should not be automatically extrapolated to the same species used in a research context. In a commercial setting, male sheep not required for breeding are routinely castrated at the time of weaning to avoid development of aggressive behaviors, prevent unwanted or unplanned offspring, and optimize meat quality, which may be tainted in mature male animals by androgens. In contrast, female animals are conventionally retained reproductively intact and are, therefore, readily available for reproductive studies. However, in a research system, cohorts of intact males and females can be retained. Secure housing and separation of males and females by dual fencing are readily achieved, while aggression is minimal between cohoused male animals kept in a consistent group from before puberty and does not cause welfare problems for these animals. Thus, sheep can be used for assessment of metabolic and behavioral outcomes that are affected by gonadal steroids, as well as those effects of prenatal environment that may differ between sexes (40, 43, 198, 213, 272, 344). Furthermore, most sheep studies of fetal development include both male and female fetuses, and often statistical analysis is performed to determine if there is an effect of sex (450). In contrast, either male or female fetuses are often selected for study in other species, although this practice is changing as the need for studying both sexes is acknowledged (96, 309).

Fact 5: Development of Major Organ and Regulatory Systems Occurs Before and Around Birth in Sheep, as in Humans, But After Birth in Rodents

Species can be classified as prenatal, perinatal (precocial), or postnatal (altricial) developers, in that most of their organ systems develop and are operational before, around, or after birth, respectively. This concept was first applied to the timing of brain development (99) and reflects the types of behaviors of which each species must be capable shortly after birth. The

trajectory of development is, therefore, both species- and organ-specific. These species-specific differences can have a substantial impact on experimental design relating to biological questions associated with periods of development. This concept applies not only to the brain, but also to most organs, although the timing of development of each organ in relation to birth is not homogeneous. In this section, we discuss some of the most-studied organs, often investigated because of their involvement in survival at birth or their importance in noncommunicable disease in adulthood, and describe the similarities and differences in development between humans and sheep.

Brain. In prenatal and perinatal brain developers, such as humans, sheep, and guinea pigs, brain mass increases dramatically before birth, and the brain is sufficiently mature to sustain fetal behavioral states by late gestation (99, 309, 382). In contrast, in rats, mice, dogs, and cats, the brain develops postnatally, with brain mass increasing and sleep states developing after birth (99, 382) (Fig. 1). The prenatal timing of brain development makes the sheep a valuable species in studies of brain development. Timing of such studies takes into consideration that the brain is more mature in fetal sheep than humans at birth: the lamb is able to move independently at birth. Consistent with earlier functional maturation in sheep, myelination of the brain is more complete at birth in sheep than humans (200) (Fig. 2*A*). The preterm sheep fetus at ~95 days gestation is at a structural and functional stage of brain development similar to that of the 24- to 28-wk-old human fetus and, at 125-130 days gestation, reaches maturity similar to a full-term human fetus (18). Sheep have also been extensively used to study perturbed brain development, for example, asphyxial and inflammatory challenges, after preterm birth (107). Importantly, studies in sheep have provided valuable understanding of processes underlying the impact of events during pregnancy and how these and clinical treatments may affect brain development and function (86).

Despite the previously mentioned advantages of working with sheep compared with rodents as a model of human brain development, a limitation is that myelination occurs earlier, in relation to birth, in the sheep than human fetus (27, 38, 292, 360). However, the overall pattern of white matter maturation in the sheep fetus provides a clinically relevant model for the developmental effects of physiological insults delaying maturation and modifying susceptibility to injury. Importantly, the maturational and perinatal brain regional injury patterns resemble those reported in human studies. Major clinically relevant insights have been derived from modeling effects of prenatal insults on the corpus callosum and white matter injury (WMI) (145, 167, 196, 287, 376, 436).

Studies on the developmental profile of the corpus callosum and the effects of glucocorticoids administered in a clinically relevant scenario at the onset of the third trimester demonstrated that betamethasone administration results in a region-specific change in the myelination of the commissural fibers of the corpus callosum (196, 376). It has been suggested that such maturational delay represents a morphological correlate to behavioral and cognitive changes known to occur in humans after prenatal glucocorticoid treatment. These studies highlight the clinical relevance of the myelination profile of the sheep fetus.

WMI in the sheep and human fetus preterm share important common histopathological and brain-imaging features. Both species share preterm vulnerability to acute and chronic WMI (18). Similar to the human fetus, the sheep fetal brain shows brain-regional WMI under conditions of moderate cerebral ischemia (18). In contrast, the brain injury pattern of rodents is not limited to WMI and includes gray matter (16, 127, 397, 434). This important species difference limits the translational relevance of rodent hypoxia-ischemia models for the study of myelination disturbances associated with chronic human WMI.

The sheep fetus displays brain hemodynamics similar to humans and, as mentioned elsewhere in this review, permits extensive instrumentation and recording (or online calculation) of physiological data, such as blood pressure, EEG, intraventricular pressure, cerebral perfusion pressure, blood oxygenation, systemic or brain regional cerebral blood flow, and protein synthesis, in the unanesthetized state. Such recordings permit study of cerebral autoregulation, an important mecha-

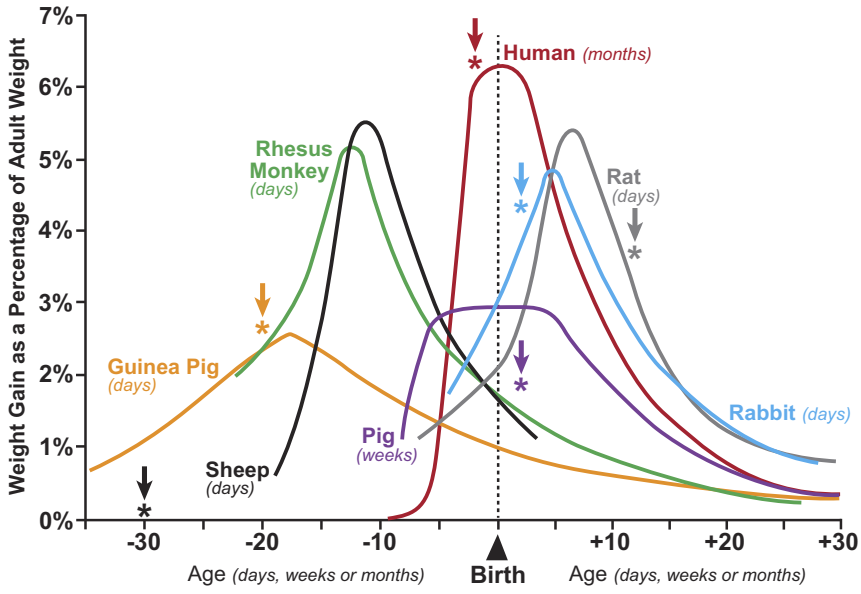

Fig. 1. Increased weight gain as a percentage of adult weight of the brain relative to birth in a range of prenatal and postnatal brain-developing species, with age of development of fetal behavioral (*) or sleep states (arrow) superimposed (134, 396, 422, 435). [Adapted from Dobbing and Sands (99) with permission.]

nism determining the outcome of WMI. The human (86, 103, 372, 409) and sheep fetus share a very limited range of cerebral autoregulation under physiological and pathophysiological conditions. Systemic hypoxia and associated hypotension result in a pressure-passive cerebral circulation (180, 192, 358, 423, 433). Infection can further exacerbate such breakdown of autoregulation and has been modeled in fetal sheep (170, 454).

Studies in fetal sheep have shown that perturbations in cerebral blood flow are necessary, but not sufficient, to explain the distribution of WMI. The developmental predilection for WMI appears to be related to both the timing of appearance and regional distribution of the susceptible preoligodendrocytes (Fig. 2*B*). When translated to the human clinical situation, ex vivo high-field MRI studies in fetal sheep suggest that current clinical MRI field strength may be a limiting factor to detect diffuse, as well as microscopic, necrosis (454).

Future studies will seek to better replicate findings in neonatal rodents in the large preterm models (125–127). Furthermore, neurobehavioral studies of preterm fetal sheep and lambs are needed to assess the sustained impact of WMI. The fetal sheep and neonatal lamb model has the potential to better mimic the neonatal care setting by including the influence of nutritional status, stressors, exposure to pain, and recurrent sedative and anesthetic exposure (54, 179, 192, 425).

Lungs. The sheep is an excellent model for investigations of human lung development for several reasons. Adult lung architecture is similar in sheep and humans, in terms of numbers of airway generations, numbers and size of alveoli, and ultrastructure of the blood-gas barrier (174, 370). Stages of lung development in sheep are similar to those in humans and occur with similar timing in relation to birth (174). Importantly, definitive alveoli first appear before birth, with ~50% of alveoli being present at full term in sheep compared with approximately one-third in humans; in rats and mice, alveoli are formed only after birth. Mature type II alveolar epithelial cells and pulmonary surfactant are present by ~0.9 full term in sheep and ~0.8 full term in humans (Figure 3) (276). In sheep, the final number of alveoli is reached at 6–12 mo after birth, compared with 1.5–3 yr in humans. Almost all available data on fetal lung fluid volume, secretion, composition, and flow dynamics have been obtained from sheep (176). Although little information has been obtained from humans and other species, the available data are generally consistent with data from sheep. Importantly, data from in utero fetal sheep have allowed a detailed understanding of the pathophysiological processes whereby intrauterine conditions chronically alter lung expansion in the human fetus (e.g., oligohydramnios, CDH, tracheopathies, and impaired fetal breathing movements) and then adversely impact lung growth and development (118, 176).

The first reliable data on fetal breathing movements were obtained from fetal sheep in utero (87). This information guided subsequent studies on humans, which showed that sheep data on factors affecting fetal breathing, such as hypoxia, hypercapnia, and hypoglycemia, could be translated to the human fetus. Furthermore, sex differences in lung development and in the respiratory transition at birth are seen in humans and sheep, especially following preterm birth (431). These sex differences in lung function at birth reflect differences in the maturation of pulmonary surfactant composition, rather than differences in lung architecture, in preterm infants (210, 410).

Several studies on the pulmonary fetal-neonatal transition support the lamb as a good paradigm for cardiorespiratory transition in newborn humans. Establishment of pulmonary function by the newborn lamb over several hours after birth, similar to the pattern in newborn humans, allows the study of particular neonatal pulmonary disorders, such as BPD and pulmonary hypertension of the neonate (8, 273, 356). In contrast, mice are mildly hypoxic immediately after birth and remain so for the 1st wk of life (373), mainly due to their relatively immature lungs at birth. Thus, most rodent models are inappropriate for studying the transition to air breathing at birth, in particular RDS, which is highly dependent on surfactant maturation. The latter mostly occurs

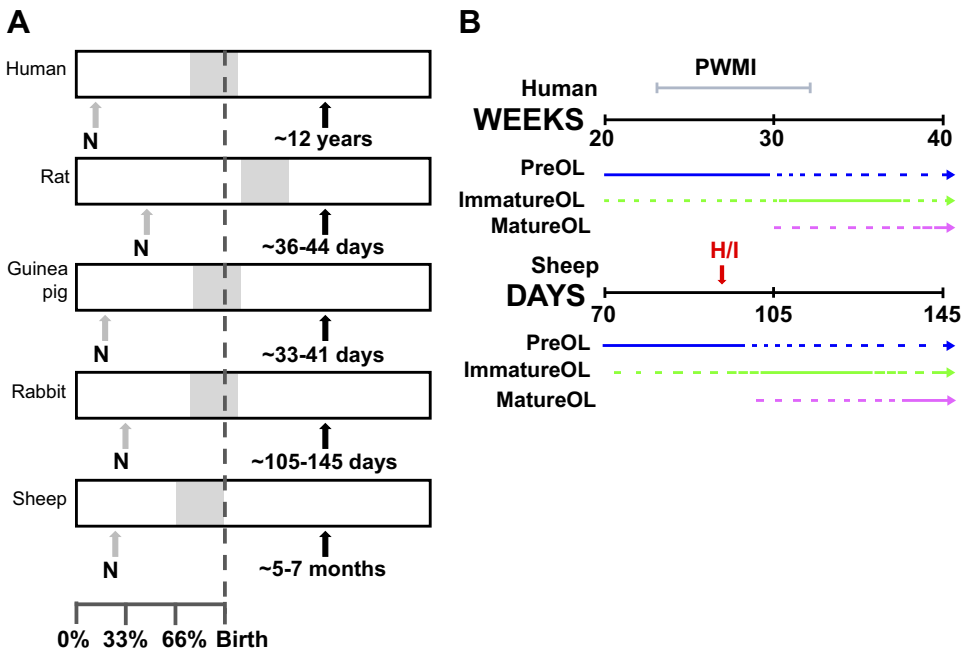

Fig. 2. *A*: timing of neurodevelopment in humans and animal models of human development. N, onset of neurogenesis; gray panel, onset of myelination; gray arrow, onset of puberty. [Republished with permission from Elsevier (200).] *B*: developmental profile of human and sheep immature oligodendrocytes (O4+ O1+). Human development is depicted during 20–40 wk based on studies of Back et al. (17, 18). The 70- to 145-day period for sheep fetal development roughly corresponds with fetal human development during the second half of gestation (383). Solid lines, developmental period when each oligodendrocyte (OL) lineage stage predominates; dashed lines, period when these stages are a minor population. Note that, in many studies, animals are exposed to hypoxia-ischemia (H/I, arrow) at 90–95 days, which coincides with the high-risk period for periventricular white matter injury (PWMI) at ~23–32 wk in humans. preOLs, late oligodendrocyte progenitors. [Republished with permission from Springer Nature for Back et al. (18).]

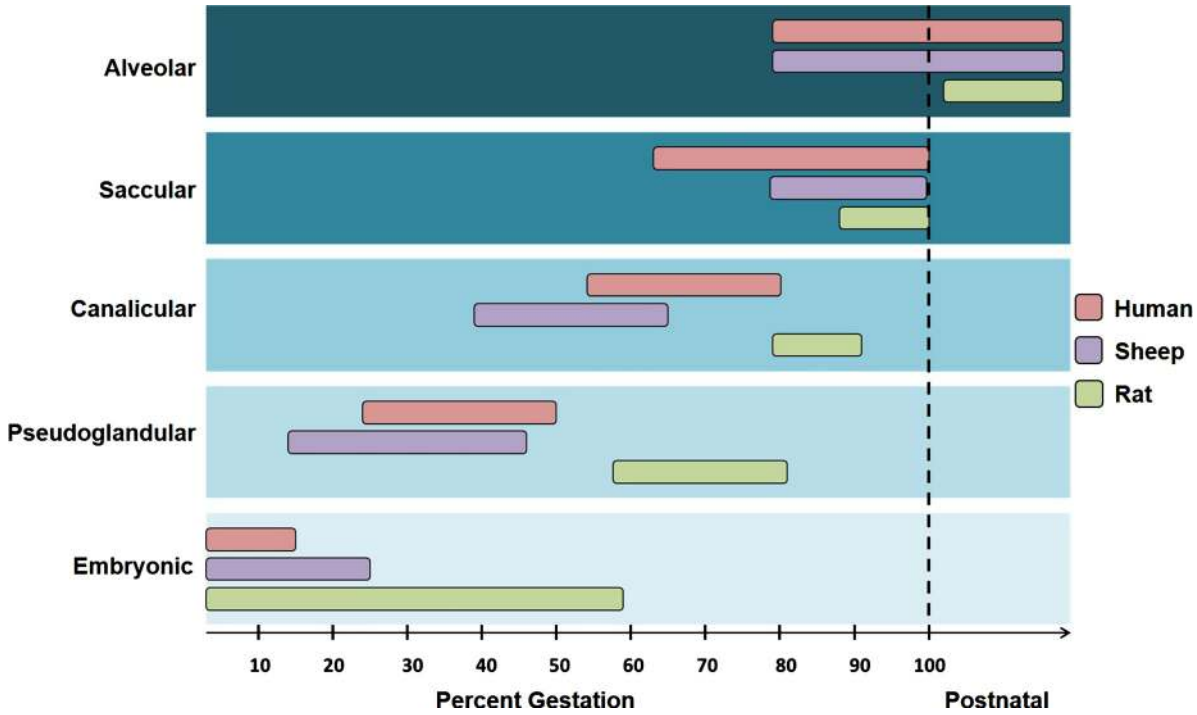

Fig. 3. Development of human, sheep, and rat lung during the 5 stages of lung development. [From Lock et al. (276).]

in the alveolar stage of development, which occurs after birth in mice and rats (Fig. 3).

Cardiovascular system. Similarly, the temporal development of the cardiovascular system of humans is more like that of sheep than rodents. This is particularly true with regard to the maturation of cardiomyocytes, the contractile units of the heart, which begin the transition from proliferative to terminally differentiated prior to birth in humans (240) and sheep (58, 223) but after birth in mice and rats (255, 408) (Fig. 4). Because humans (37) and sheep (222) have limited capacity to generate new cardiomyocytes after birth, this difference may result in lifetime retention of cardiomyocytes that have been altered by environmental insults in utero throughout their life (310, 447, 448, 450, 451, 453). In rats, cardiomyocyte proliferative capacity is lost 7–10 days after birth (255); thus there is a capacity to replace lost or altered cardiomyocytes in the early postnatal period (268).

Similar temporal differences between species are observed for the maturation of the cardiac autonomic nervous system. In rats, cardiac sympathetic fibers are not present until after birth (271). However, in sheep and humans, cardiac innervation occurs in utero (252). Furthermore, an increase in regulatory control of heart rate by the parasympathetic nervous system occurs in the last third of gestation in humans (475) and sheep (274, 445), evidenced by a slowing of heart rate and an increase in heart rate variability, but this occurs postnatally in rats (432).

The sheep has proven to be an excellent model for chronic preparations for maternal, placental, fetal, and neonatal vascular function studies. Several authors have implanted flow probes to determine blood flow to different vascular beds in conditions such as hypoxia and oxidative stress (183, 186, 226, 428). Microspheres injected into the fetal bloodstream have been used to provide a precise determination of the distribution of combined cardiac output and its redistribution in physiological or disease states (186, 188, 312, 368, 393), a technique that enabled better understanding of fetal cardiovascular function. MRI has also been employed to measure fetal cardiovascular function, including cardiac response to infarct and blood flow in major vessels to measure distribution of cardiac output

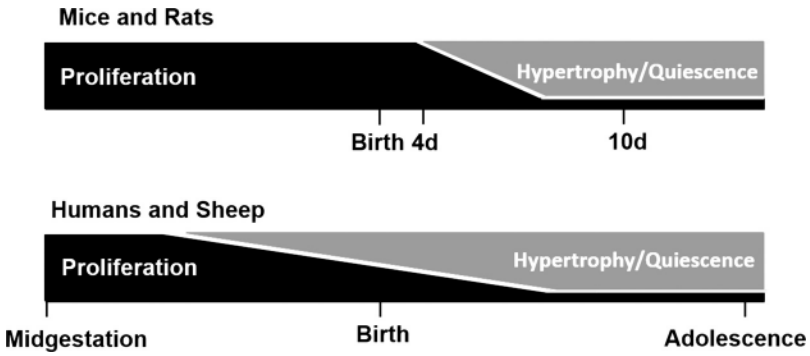

Fig. 4. Transition from cardiomyocytes that contribute to growth of the heart by proliferation to those that contribute by hypertrophy occurs after birth in rodents but before birth in humans and sheep (58, 255, 408). [Adapted from Lock et al. (277) and Morrison et al. (316).]

(104); however, anesthesia is required. For technical reasons, a relatively large animal, such as the sheep, is well suited to these cardiovascular techniques, which are very challenging in small animals, such as rodents and chickens (325). Another important issue for investigating vascular function is access to resistance arteries, usually after four or five branches from the main conduit vessel. These small (<200- to 500-μm internal diameter) arteries control the flow resistance in an organ and are the most important determinants in impairment of the circulatory system (352). Several ex vivo studies using wire or pressure myography in sheep have described the developmental function of resistance arteries in vascular beds, including mesenteric, femoral, cerebral, and pulmonary (273). The access to different types and sizes of vessels from large animals allows scientists to better understand vascular function and mechanisms underlying clinical observations in humans.

Glucose metabolism. One of the important differences between adult humans and sheep is their source of energy. In humans, energy is directly derived from glucose, primarily supplied by ingested starch or from the intracellular breakdown of stored fatty acids and glycogen (3, 171, 470). Ruminants, such as sheep, obtain energy primarily from short-chain volatile fatty acids, such as acetate, propionate, and butyrate, absorbed from the gut. These fatty acids are produced in the rumen by the action of rumen microorganisms, which anaerobically metabolize the complex polysaccharides of ingested pasture (15, 171, 270, 341). The precursors for fatty acid synthesis in humans and ruminants are glucose and acetate, respectively (15). In humans, fatty acid synthesis primarily occurs in the liver; in ruminants, it occurs in adipose tissue (15, 171), as well as in mammary tissue of lactating animals (15). Despite these metabolic differences, there are substantial similarities of the regulatory systems within human and ruminant tissues that govern energy homeostasis. Furthermore, before birth and microbial colonization of the rumen, the main energy source for the sheep fetus is glucose supplied across the placenta (28), as it is for the human fetus. Transition to free fatty acids as the main energy source in sheep occurs after birth with establishment of the rumen. Importantly, for studies of neonatal nutrition, the neonatal lamb remains functionally monogastric, rather than being a ruminant. Closure of the esophageal groove occurs as part of suckling behaviors exhibited when young lambs drink milk from a teat or from the ewe (456). This process is mediated by vagus nerve activity and allows milk to bypass the reticulum and rumen and directly enter the abomasum (331, 456). Bacterial colonization of the rumen begins within the first 2 days after birth in lambs reared with their dams, and cellulolytic bacteria appear within the 1st wk or so of life, even before the lambs begin to consume solid feed (128). Bacterial numbers in the rumen continue to increase and the proportions of bacterial types continue to change throughout the first few months of life (128). Concentrations of volatile fatty acids in rumen contents, derived from bacterial digestion in the rumen, are minimal at 3 days of age and increase gradually until ~8 wk of age, indicating a gradual transition in energy source and metabolism from nonruminant to ruminant over this period (366).

Similarities between sheep and human metabolism are further evidenced from metabolic pathway reconstruction using genes encoding metabolic enzymes based on a draft bovine genome sequence (>98% homology of the ovine with the bovine genome sequence) (398). Although the analysis was impacted by the draft nature of the bovine genome sequence, ≥86% of all mammalian biochemical pathways were identified in the cow (i.e., the percentage of potential pathway "holes" was 14%). In particular, ruminants and nonruminants have similar regulatory and enzymatic components for lipogenesis, lipolysis, and adipogenesis (100, 329, 398). For example, the leptin signaling pathway and its tissue-specific functions orchestrating satiety appear to be very similar in humans and ruminants (45, 65, 69, 70). Similarly, the key transcription factors controlling the expression of a cascade of genes in white and brown adipose tissue (WAT and BAT, respectively) are generally highly conserved between humans and sheep [96% peroxisome proliferator-activating receptor-γ (*PPARG*), 87% PR domain-containing protein 16 (*PRDM16*), and 97% signal transducer and activator of transcription 5A (*STAT5A*) amino acid conservation (unpublished data)]. Therefore, it is likely that differences in energy regulation between mammalian species are primarily mediated by changes in input signal timing and intensity and the magnitude and range of tissue responsiveness, rather than major architectural modifications in biochemical and signaling pathways.

The timing of development and functional maturation of insulin-secreting β-cells in the pancreas occurs predominantly before birth in sheep, as in humans, but extends into the suckling period in the rat. Insulin-producing cells can first be detected histologically at ~25% of full term in humans and sheep, but these cells do not appear until ~60% of full term in the rat (377). Functional maturation, including development of glucose-responsive insulin secretion and increasing insulin abundance, occurs before birth in sheep (129, 465) and humans (227, 348, 365), but remodeling and maturation of the pancreas occur postnatally, at 1–2 wk of age, in the rat (394).

Hepatic drug metabolism. In humans, the fetal liver has a limited capacity to metabolize drugs compared with the adult; for example, there is lower mRNA expression of the cytochromes *P*-450 *CYP2C9*, *CYP2C19*, and *CYP3A4* (191). With increasing gestational and postnatal age, expression of these cytochrome *P*-450 enzymes increases (191). The same is true in the sheep. Cytochrome *P*-450 enzyme expression is lower in fetal and newborn than adult sheep (369). mRNA expression of *CYP2C19*, *CYP2D6,* and *CYP2A6* is lower in fetal than adult sheep (369), and cytochrome *P*-450 protein expression is lower in lambs than adult sheep (141). Microsomes extracted from frozen liver tissue have been used to show lower capacity to metabolize rosiglitazone, a CYP2C9 substrate, in the fetal than adult sheep liver (33). This similar ontogeny of drug-metabolizing enzymes in sheep and humans enables use of the sheep as a model to determine the timing of development of specific drug-metabolizing systems. In addition, by using the chronic catheterized sheep, drug concentrations can be measured in the maternal and fetal blood and amniotic fluid over a prolonged period of time (32, 314), which is an advantage over small-animal models or human studies. Additionally, the sheep model has been used to study maternal drug use and its effect on the fetus (314, 315).

Fat phenotype. In mammals, there are typically three types of adipose tissue: WAT, BAT, and beige adipose tissue. These tissues are functionally, morphologically, and developmentally distinguishable. WAT has primary responsibility for storage of energy in the form of triglycerides, while BAT and beige

adipose tissue have thermogenic capabilities, as well as roles in energy homeostasis (9, 418). Beige adipocytes are typically induced within WAT depots. BAT is present as discrete depots in hibernating mammals and the young of most mammals (excluding pig), protecting them from hypothermia by generating nonshivering thermogenesis. Mammalian species show remarkable differences in the developmental timing of BAT (418–420). Altricial mammals, such as mice and rats, develop BAT postnatally, in parallel with development of the hypothalamic-pituitary-adrenal (HPA) axis, and maintain BAT throughout life. In contrast, humans and sheep, which produce precocial young, develop BAT in the last third of gestation, again, in parallel with development of the HPA axis, and this BAT is metabolically activated by cold- and birth-related hormones in the immediate postnatal environment. Within a relatively short period after birth, activity of the HPA axis in humans and sheep declines and, correspondingly, most BAT depots disappear, with some replaced by WAT (367). Thus, in contrast to adult rats and mice, adult humans and sheep have little BAT. It should also be noted that percent body fat at birth is higher in humans (16%) than sheep (2%), partly due to greater placental transport of fatty acids (297).

HPA axis. In all mammalian species studied to date, with the exception of rats and mice (76), circulating glucocorticoid concentrations increase in plasma of fetuses approaching full term (124, 132, 285) (Fig. 5). The magnitude and timing of this preparturient surge in fetal plasma glucocorticoid vary between species and may be a result of activation of the fetal HPA axis (67) and/or reductions in levels of plasma corticosteroid-binding proteins (66, 472) and/or an increased transplacental flux of glucocorticoids from the maternal to the fetal circulation (250). The preparturient surge in fetal plasma glucocorticoid concentration is important for regulation of structural and functional maturation of a number of fetal organs, promoting a switch from tissue accretion and cellular proliferation to tissue differentiation (130, 132). This prepares fetal tissues, homeostatic mechanisms, and physiological systems for the successful transition to neonatal life and independent survival ex utero (132, 266, 412).

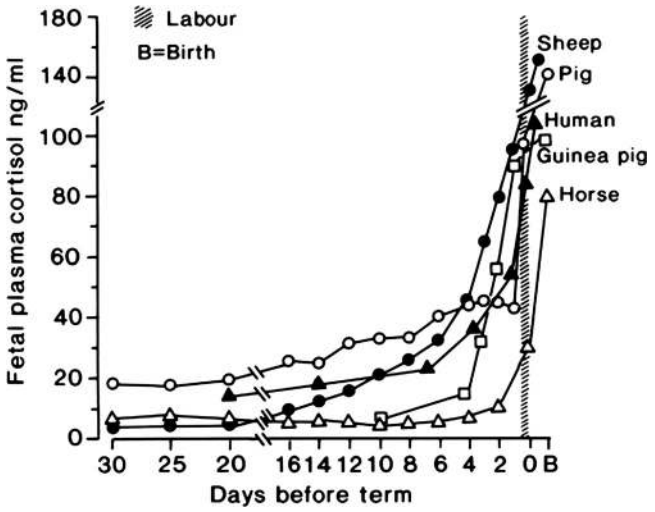

Fig. 5. Mean fetal concentrations of plasma cortisol with respect to time (days before birth) from delivery in sheep (●), pig (○), human (▲), guinea pig (□), and horse (△). [From Fowden et al. (132) and reproduced with permission.]

Importantly, the timing of the fetal plasma glucocorticoid surge is very similar between sheep and humans (Fig. 5). In contrast, in precocial species, such as the rat and mouse, the plasma glucocorticoid surge occurs postnatally (286). Consequently, rodent species are born with a high degree of prematurity, and the postnatal rat is an established model of human prematurity, inasmuch as postnatal development of physiology in this species compares with prenatal milestones in the human (303, 403, 455). In marked contrast, the sheep provides an excellent model for investigation of glucocorticoid-induced maturation of several key fetal organs and systems before birth in humans.

Thus, there is clear evidence that the timing, in relation to birth, of the maturation of major organ systems is more similar between humans and sheep than between humans and rodents.

Fact 6: 'Omic Studies in Sheep Are a Helpful Tool in Understanding Complex Gene-Environment Interactions

Use of high-resolution genetic maps [https://www.hgsc.bcm.edu/other-mammals/sheep-genome-project (216)] to sequence and assemble the sheep genome onto chromosomes has allowed much faster development of methodologies for studies of ovine gene expression in recent years. In addition to real-time PCR, RNA sequencing (RNA-Seq) and microarrays have been utilized to measure gene expression in sheep tissues (146, 243, 375, 381, 443). In addition to coding genes, RNA-Seq and custom-designed microarrays have also been used to measure microRNA expression in sheep (260–262, 316). The ability to perform fetal surgery to monitor and manipulate the fetus and then collect tissue for primary cultures and RNA-Seq, particularly the ability to relate these in vivo physiological measures and analysis of blood samples in the same animals, is unique to the use of sheep as an animal model (Fig. 6) (62, 75).

Extant mammalian species have evolved different numbers of chromosomes, different relative positions of centromeres, and large-scale intra- and interchromosomal rearrangements and translocations (117, 480). The mouse and rat large-scale genomic organizations are more dissimilar to the human genome than are most other mammalian genomes (117, 216, 241). The evolution of mammals can be traced through the mapping of conserved syntenic blocks, i.e., conserved genomic regions containing a contiguous order of genes on a chromosome, reflecting a common ancestral origin (Fig. 7). Because of their relatively recent evolution from a common ancestor, the sheep and cow genomes show a high level of chromosomal structural conservation (i.e., large syntenic blocks), although there are some species-specific differences (117, 216). Comparisons of ruminant and human genomes show substantial numbers of chromosomal rearrangements, although these pairs retain large syntenic blocks (117, 216). The rat and mouse genomes, however, have undergone substantially more chromosomal, particularly interchromosomal, rearrangements than the human (or ruminant) genome (117). The evolutionary distance between species can be quantified by measurement of reversal distance for these chromosomal rearrangements, i.e., the minimum number of reversals of major syntenic blocks that transforms one genome into the other (401). Use of a coarse chromosomal resolution shows the reversal distance between recently diverged species, such as chimpanzee and human, to be relatively low (11 units). The cow-human comparison has a

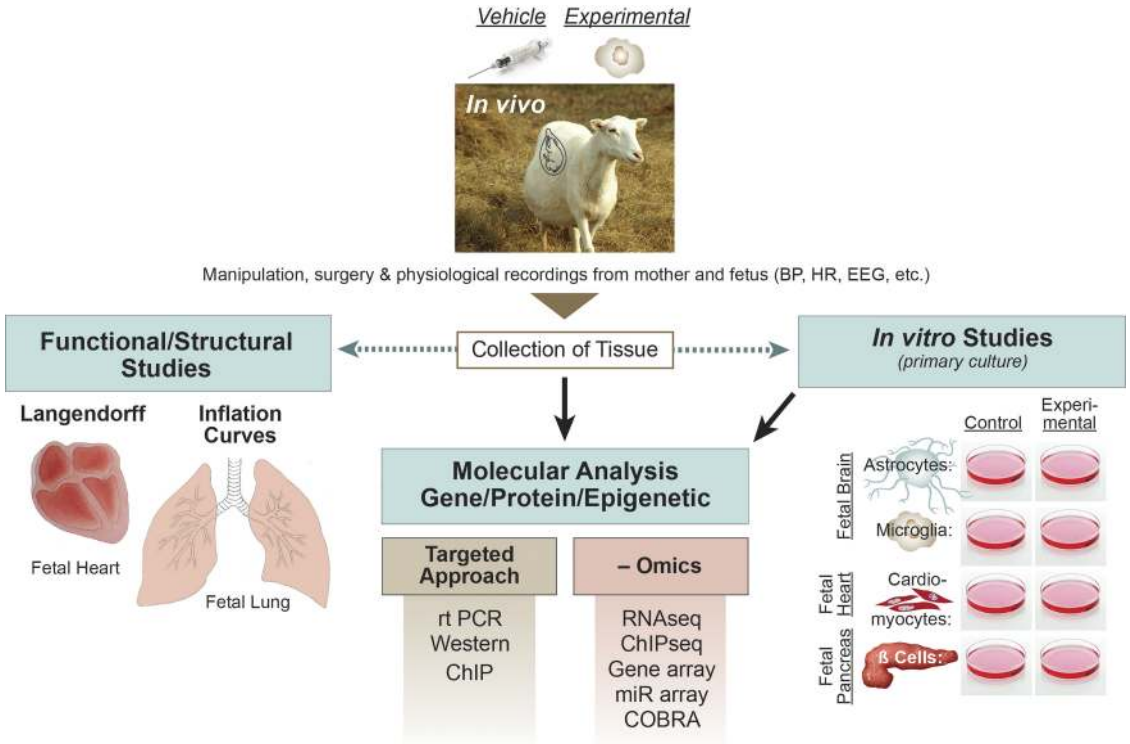

Fig. 6. Studies can be performed in the sheep fetus in utero, and then tissue [e.g., brain (astrocytes and microglia) (75), pancreas (isolated islets), or heart (cardiomyocytes)] can be collected for molecular analyses (316), in vitro primary cell culture (449), ex vivo functional studies, or structural studies (51). BP, blood pressure; HR, heart rate; EEG, electroencephalogram; rt PCR, real-time polymerase chain reaction; ChIP, chromatin immunoprecipitation; miR, microRNA; COBRA, combined bisulfite restriction assay.

much larger reversal distance (185 units), but this is, nevertheless, significantly less than the mouse-human and rat-human comparisons (262 and 261 units, respectively). Thus, mouse and rat comparisons with humans are more divergent than cow (and, likely, sheep) comparisons with humans. Because chromosomal rearrangements during evolution may disrupt long-range genomic connectivity between distal regulatory elements and genes, these rearrangements have the capacity to alter coordinated regulation of multiple genes within these genomic domains (327). Indeed, these chromosomal structural changes are likely to be important features of speciation. The human ENCODE project used chromosomal conformation and chromatin modification analyses to map many types of multigene chromosomal domains that show coordinate regulation of gene expression (119, 229). Coordinated gene regulation is important in developmental programs, tissue-specific patterning, and responses of genes to environmental influences. The greater extents and types of chromosomal rearrangements in rat and mouse than other mammals indicate that they are poorer model organisms for understanding coordinated multigene regulation within large chromosomal domains in humans. The extent of nucleotide conservation of ruminant genes with single-copy human orthologous genes is also greater than that of mouse and rat genes (117). The short generation times of rats and mice are postulated to cause higher rates of mutation in these species, which may underlie the higher levels of gene sequence diversity and chromosomal structural alterations of rats and mice than other mammals (256).

There is considerable interest in complex genetic traits in humans. Genetic predisposition to complex traits often interacts with strong environmental factors, which together define the overall probability of trait occurrence. For most cases, how this interaction occurs is unclear. Complex genetic traits in all species are polygenic, with only a small contribution from each gene. The genetics of complex traits are analyzed using genome-wide association studies, which typically require high-density single-nucleotide polymorphism (SNP) chips (~800,000 SNPs) and very large phenotyped populations (typically tens to hundreds of thousands of outbred individuals) to obtain sufficient statistical power and genome resolution (471). High-density SNP chips and very large phenotyped populations are available from the cattle and sheep industries, which have facilitated extensive genome-wide association analyses to identify ovine and bovine genomic regions and genes contributing to a variety of production traits. This approach has identified several genes contributing to complex traits, such as body size in ruminants, that also contribute to similar complex traits in humans (7). Thus, ruminant genetics may help inform the human genetics contributing to complex traits and also aid in understanding how interactions between genetics and environment underpin these traits. The lack of availability of very large outbred populations of rats and mice limits similar studies in these model species.

Fact 7: Epigenetic Responses in Sheep to an Altered Perinatal Environment Can Be Usefully Explored Across Different Time Periods in Development

In contrast to genetic mutations, epigenetic changes occur in the absence of alterations in the underlying DNA sequence,

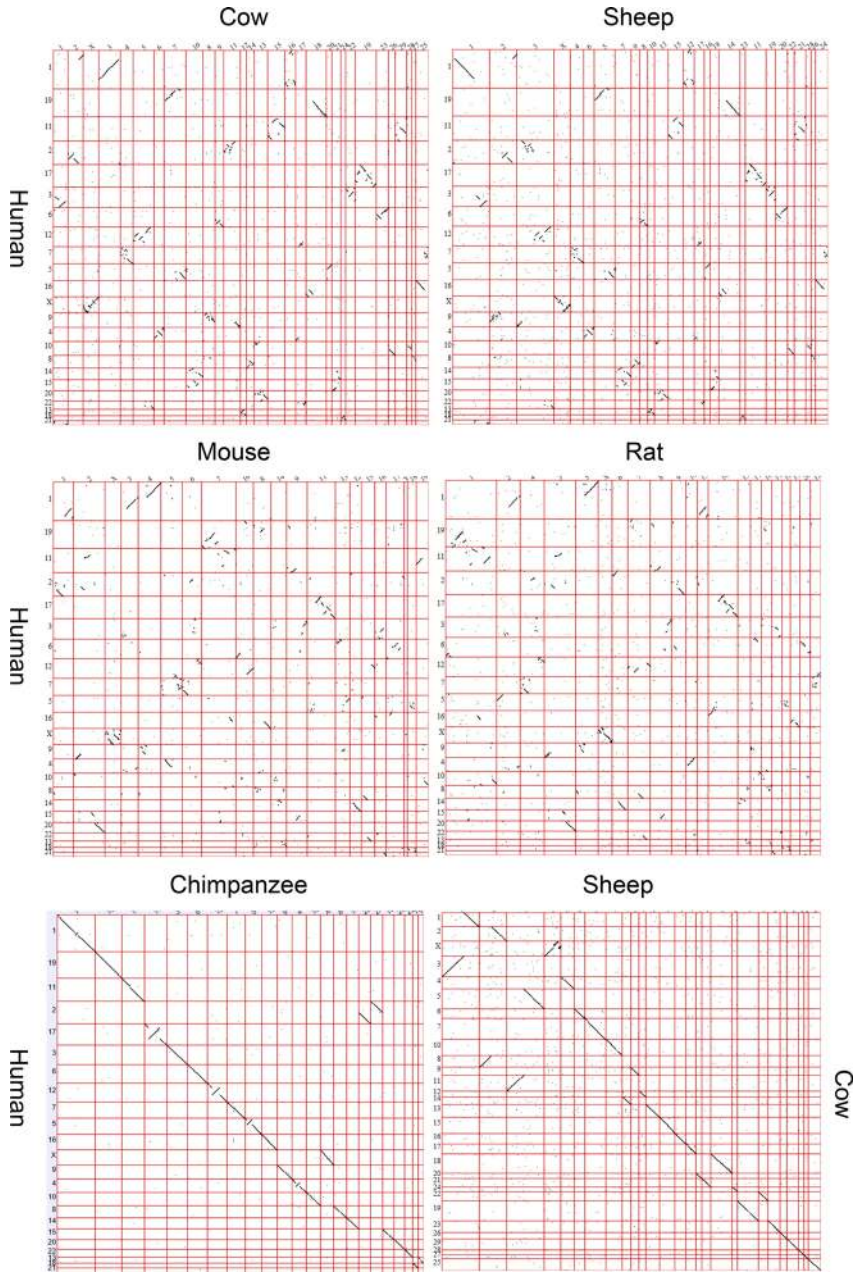

Fig. 7. Conserved syntenic blocks for all chromosomes identified at coarse resolution by pair-wise species comparisons of chimpanzee, cow, sheep, mouse, and rat genomes with the human genome. Cow and sheep comparisons with the human genome generally show larger syntenic blocks than mouse and rat comparisons with the human genome. Pair-wise matrices were constructed using Genomicus (283).

and an increase or a decrease gene expression can be reversible. Epigenetic changes are primarily due to methylation of DNA, microRNAs, and chemical modifications of DNA-associated proteins called histones. The Encyclopedia of DNA Elements (ENCODE) project has mapped a wide range of epigenetic modifications at nucleotide resolution in a broad spectrum of human and mouse tissues and cells (119). The project identified many novel and overarching epigenetic structural and functional modifications that are conserved in other mammalian tissues. This data-rich information resource is continually updated, and a significant amount of the human and mouse epigenetic information has been successfully transposed onto the genomes of cattle and sheep (334). This transposed information agrees well with a small selection of epigenetic data independently generated using sheep and cattle tissues. There is, however, inevitable information loss in this process, caused by limitations in the ability of the sequences used to be mapped, to define epigenetic modifications across the mammalian species and species-specific modifications. The recent Functional Annotation of Animal Genomes (FAANG) initiative has begun to generate high-resolution epigenetic maps for a number of mammalian production species and tissues, especially sheep and cattle (13), and will provide additional detailed species-specific information. Genome-wide mapping of specific chromatin modifications and DNA methylation in a limited tissue range from sheep and cattle has also been undertaken (59, 441, 444).

Confirmation of the functional importance of these epigenetic changes for sheep, as shown in rodents and humans, has also been provided through a number of smaller-scale studies demonstrating regulation of specific genes through DNA methylation and histone modifications in fetal sheep tissue (450,

452, 476, 477). This approach has also been taken to determine if these mechanisms are involved in programmed effects on the fetus that persist after birth. DNA methylation has been shown as a programming mechanism for blood pressure and glucose tolerance in such sheep studies. For example, 21-day-old low-birth-weight lambs have higher expression of insulin-like growth factor 2 (*IGF2*) receptor (*IGF2R*) due to increased acetylation of histone H3K9 at the *IGF2R* promoter (452) without changes in DNA methylation (453). In contrast, undernutrition in the periconceptional period decreased *IGF2* gene expression in the adrenal gland of lambs 4 mo after birth due to decreased DNA methylation in the proximal CTCF-binding site in the differentially methylated region of the *IGF2/H19* genes (477). Furthermore, DNA methylation changes were also observed in fetal liver exposed to periconceptional methyl donor-deficient diets. Sinclair et al. demonstrated that clinically relevant deficiency of vitamin B_{12}, folate, and methionine at the time of mating in sheep caused epigenetic modifications to genes associated with blood pressure, insulin resistance, obesity, and immune function (400). This study also showed sexually dimorphic effects, with males displaying increased DNA methylation and more adverse adult phenotype. These studies demonstrated the importance and potential of the sheep to study the reversibility of epigenetic modifications by nutritional therapeutics or interventions during pregnancy. Like humans, sheep are a large outbred species with similar timings of pre- and postnatal development. Studies in humans continue to further our understanding of epigenetics. However, because of the practical and ethical limitations of using humans, sheep offer both a wider scope for sampling during pregnancy and greater potential for controlled studies at different time points in gestation.

Genetic imprinting is a special case of epigenetic control of gene expression where one copy of a gene is imprinted (silenced) and the other is expressed in a parent-of-origin-specific fashion. Genes that promote fetal growth tend to be expressed from the paternal allele, while those that inhibit fetal growth are expressed from the maternal allele. Thus, imprinted gene expression in offspring is said to reflect genetic conflict between paternal and maternal genomes. Examples of these are *IGF2* and its specific receptor *IGF2R* (462). *IGF2* is expressed from the paternal allele and promotes placental and fetal growth in all mammalian species studied, while *IGF2R,* which inhibits fetal growth, is imprinted in most species, but not in human placenta (56). Because the complete complement of imprinted genes in sheep has not been defined, comparisons with other species are difficult.

Fact 8: CRISPR Technologies Open New Windows of Opportunity for Genetic Manipulation Studies Performed in Sheep

Genetic studies in multiple mammalian species, including humans, have shown associations between species-specific genetic variants and a wide range of simple and complex traits. In particular, hundreds of health-related human genetic associations have been discovered (442). However, there is a major limitation in proving that these human genetic variants are causal, and there is generally very poor understanding of how causal genetic variants affect gene function and phenotype, especially when the variants are located in presumed regulatory elements positioned outside protein-encoding exon sequences. This limitation can only be resolved by genetic manipulations in animal models.

Conventional genetic engineering technology and various mRNA suppression technologies used over the last 20 years have been successfully applied to several large-animal models, including sheep (Table 2). For example, mRNA knockdown using a lentiviral-mediated short-hairpin RNA was used to demonstrate that suppression of chorionic somatomammotropin hormone in sheep caused IUGR, impacting placental and fetal liver development (20). Related studies using similar technologies demonstrated that proline-rich 15 (*PRR15*) mRNA in the ovine trophectoderm is essential for embryo viability (142, 374). However, the majority of studies have been confined to the mouse and rat because of their greater technological compatibility, shorter generational times, and lower costs. The recent development of CRISPR and related genome-editing technologies enables rapid and precise genetic modification of the genome (4). CRISPR technology is more versatile than conventional genetic engineering, as it can add, subtract, or substitute DNA with precision in the genome of any animal. This ability enables easier and faster engineering of a genetically modified animal for investigation of gene function and regulation. The impact of the technology is evidenced by 11 publications using CRISPR technology in sheep in 2017 compared with none in 2016 and widespread application of the technology in most large domestic animal species (249).

One application of CRISPR technology is introduction of a genetic variant associated with human disease into the approximate homologous region in the genome of a large-animal model for investigation of the variant's gene regulatory function and associated phenotype, thereby informing human health. Another application is the engineering of sheep as models for investigation of human neurodegenerative diseases (318). Moreover, traditional selective breeding of animals by humans over the last 10,000 years of domestication radically altered the form and function of these animals and generated a highly informative genetic resource for understanding the genome-phenotype relationship. This human-directed evolutionary process selected for advantageous natural allelic variants in the population, but this is limited by the extent of genetic variation available for selection in the founding population and the slow pace of generational changes. CRISPR technology can be used to more rapidly introgress favorable natural alleles or de novo genetic variants into large populations of livestock animals, thereby boosting their value. One example is production of sheep with an inactivating mutation in the myostatin gene that results in skeletal muscle hypertrophy (77); other examples include genetic alterations to a range of genes impacting reproductive performance (55, 479), adipose tissue deposition (55, 339), and wool color and length (195, 257, 478). Moreover, genetic variants associated with, for example, growth, metabolic, and reproductive traits in large-animal species may highlight human genes and genetic variants that impact similar functions. Thus there has been a rapid update of gene-editing technology for multiple purposes in sheep, some of which will make the sheep a very useful model of human disease.

Fact 9: Sheep Can Be Used in Neurodevelopmental Studies Owing to Similarities Between Stages of Brain Development in Sheep and Humans

Current research in sheep models is informing clinical practice by developing an understanding of how clinical interventions may interact with other exposures such as hypoxia to affect neurodevelopmental outcomes (251). As discussed above, the capacity to instrument and then directly study the nonanesthetized fetal sheep, including continuous measures of fetal neurophysiological responses to in utero events, hypoxia, and maternal drug administration, is a particular advantage of the sheep for such studies (311, 313). Preclinical sheep models also allow initial testing of interventions to improve neurodevelopmental outcomes, such as melatonin administration, which has been evaluated in studies aiming to reduce brain damage after birth hypoxia (474), chronic neonatal hypoxia (183), and IUGR (301). Positive findings in the preclinical model of IUGR led to evaluation of melatonin in pilot human clinical trials (301), again demonstrating the potential for translation from sheep to human pregnancy.

Another emerging application for fetal sheep models in the study of the programming of neurodevelopment is the evaluation of the impact of maternal stress during pregnancy, which is achieved by intermittent and unpredictable maternal isolation in the last trimester (102). Isolation is also used as a stimulus in progeny tests characterizing effects of the maternal environment (e.g., periconceptional undernutrition) on later postnatal HPA axis development in juvenile and adult sheep (182). The sheep has also proved a useful model for studies of postnatal learning and the functional impacts of altered neurodevelopment (74). Complex learning requiring executive function, including learning to associate specific shapes and colors with rewards and reversal learning requiring animals to learn changes in these cues, has been demonstrated in sheep (74, 317). Appropriate habituation to handling and test conditions is required, and prior experience needs to be consistent between animals, since sheep remember maze-learning tasks (181, 199), as well as faces (236), for at least several months.

Fact 10: Many Important Placental Physiological Characteristics Are Shared Between the Sheep and Human

The mammalian placenta is best known for its critical role in maternofetal gas, nutrient, and waste exchange. It also orchestrates maternal physiological adaptations to pregnancy essential to pregnancy success by secreting abundant steroid and peptide hormones and promoting immune tolerance of the conceptus. For the purpose of brevity, this section focuses on comparisons between sheep and humans as they relate to gas (O_2) and selected nutrient (glucose, amino acids, and fatty acids) exchange and metabolism. One of the unique advantages of the sheep is its large size, which allows placement of catheters to facilitate collection of serial blood samples from both maternal and fetal sides of the placental barrier in an unanesthetized state. This facilitates the in vivo unstressed study of placental metabolism (459), which at times is at odds with ex vivo preparations (395). Utilization of these in vivo preparations has permitted unique insight into real-time in vivo placental gas and nutrient consumption and transport and has highlighted a number of important physiological similarities between sheep and human placenta (1, 353), despite obvious structural differences.

Placentas are classified based on their gross anatomic appearance (shape), as well as the type of exchange interface and interdigitation of fetal chorionic villi with the endometrium. The latter is a histological classification based on the maternal tissue layer in contact with the fetal chorionic epithelium (trophoblast). The differences between sheep and human gross and histological types have often been thought to limit the potential translation and relevance of studies on sheep placenta. However, a number of important gas and nutrient exchange parameters highlight similar function and metabolism between the sheep and human, rendering the sheep a useful model in terms of placental function.

The placenta is defined as the apposition or fusion of the fetal trophoblast with the maternal endometrium (228). The chorionic villi form the interface between the maternal and fetal circulations. In humans and some primates, rodents, and rabbits, the placenta is classified as discoid (a single disk-shaped exchange organ) and hemochorial. In the hemochorial placenta, originally described by Grosser (136, 228), the fetal chorionic epithelium (trophoblast) is bathed in maternal blood, as the fetal chorionic villi have extensively eroded through the maternal uterine luminal epithelium, endometrial connective tissue, and endothelium, exposing them to maternal blood. However, there are variations in the number of intervening trophoblast layers. In humans, the placenta is hemomonochorial, while in the mouse, a species often used for placental studies, the placenta is hemotrichorial, with three intervening trophoblast layers. In addition, the mouse placenta is labyrinthine, in contrast to the villous structure of the human placenta.

Other mammalian species have placentas with different gross and histological structure. Ruminants, such as sheep, have a cotyledonary (multiple, discrete areas of attachment for exchange) placenta that is synepitheliochorial in nature (473). In sheep, chorionic villi (fetal tissues) become highly interdigitated with the maternal endometrium, and fetal trophoblast binucleate cells cross from the fetal epithelium and fuse with maternal luminal epithelial cells to form a fetomaternal syncytium. However, these cells never cross the maternal epithelial basement membrane. In early pregnancy, the developing chorionic villi, which together constitute the fetal cotyledons, associate with specialized sites within the uterus, termed caruncles, which are well-vascularized regions of nonglandular endometrium (380). Together, the cotyledon and the caruncle are termed a placentome.

Independent of differences in shape and interhemal membrane interaction, one of the major structural similarities between human and sheep placenta is the architecture and function of the villous tree surrounded by the trophoblast. The villous tree is the core of the functionally relevant microarchitecture of the placenta. In both species, the villous tree is divided into stem, intermediate, and terminal villi, all of which contain appropriate fetal stem arteries and veins, intermediate arterioles and venules, and terminal capillaries. In the sheep, the epitheliochorial surface folds to form these villi, and on the fetal side, each villus has a central arteriole, which gives rise to a number of branches. Studies examining the pattern of placental perfusion highlight that both the sheep and human placenta display properties of a venous equilibrator, i.e., maternal and fetal blood flow in a parallel (concurrent) direction

(122), giving rise to the near equalization of the venous streams of maternal and fetal circulation (29, 458). However, equilibration cannot occur, because the transplacental diffusion of O_2 is across a placenta (trophoblast) that consumes O_2 (29). In a human study examining uterine-umbilical saturation and venous P_{O_2} differences, uterine and umbilical venous blood was sampled during cesarean section (135), and the normal uterine-umbilical P_{O_2} difference near term was determined to be ~10 Torr, which is comparable to the ~14-Torr uterine-umbilical venous P_{O_2} difference in sheep (461). This concurrent perfusion pattern is in contrast to horse, rabbit, and guinea pig placentas, which display countercurrent exchange, where fetal and maternal blood flow in opposite directions and efficiencies in exchange are encountered as the venous output equilibrates with or exceeds the arterial input of the other stream (458).

Adequate nutrient delivery to the fetoplacental unit relies on adequate placental perfusion. During pregnancy, both sheep and human placenta display progressive increases in weight (as well as an increasing fetal-to-placental weight ratio). Uterine blood flow increases to a similar extent in humans (2.5-fold) and sheep (3-fold) over gestation (29). O_2 crosses the placenta by simple diffusion and is limited by blood flow (460). The transplacental P_{O_2} gradient (the driving force for O_2 diffusion) in these two species is relatively similar near term: indwelling catheter data collected from sheep pregnancies (378, 458) mirror cordocentesis data collected from human pregnancies (29, 353). Furthermore, O_2 consumption of the human placenta is similar to that of the sheep placenta near term (37 and 34 $ml \cdot min^{-1} \cdot kg$ fetal wt^{-1}, respectively) (48, 297), and O_2 consumption by both human and the sheep placenta is ~40% of total uterine O_2 uptake (64). This high placental O_2 consumption facilitates fetal O_2 supply across the basal membrane of the trophoblast and, importantly, placental oxidative phosphorylation of glucose, yielding ATP, and promotes placental transporters and hormonal synthetic properties (395). Indeed, the fractional protein synthesis rate of the sheep placenta has been determined in vivo to be ~60%/day (64) compared with 30%/day in human ex vivo studies (64).

In addition to O_2, glucose is a key nutrient for placenta metabolism, and its transport and metabolism share similarities between the sheep and human placenta. Glucose is the primary substrate for fetal development, and a reliable placental supply is necessary, given that human and sheep fetuses normally have no detectable capacity to produce glucose, while in both species supply is driven by a maternal-fetal gradient (97, 178). Placentas of both species express similar facilitative glucose transporters (SLC2A1, SLC2A3, and SLC2A8) (269, 284, 411). A number of other members of this family of glucose transporters (SLC2A4, SLC2A8, SLC2A9, and SLC2A12) have been identified in the human placenta (411), and further investigations of their presence in the sheep placenta are warranted. These transporters facilitate glucose movement down a concentration gradient through the maternal-facing membrane of the microvillous membrane, through the trophoblast and fetal endothelium, into the fetal circulation by moving through the basal membrane trophoblast layer facing the fetus. As in the case of O_2, the placenta of both sheep and humans consumes large amounts of glucose (~60–80% of uteroplacental uptake) (97). In common with the human placenta, the sheep placenta converts large amounts of glucose to lactate to further accentuate the transplacental gradient and also lock carbohydrate into the fetal/placental compartment (28, 346).

In fetal life, concentrations of fructose relative to glucose are significantly higher in sheep than human fetuses, although at birth fructose concentrations fall rapidly to trace levels. It is plausible that this reflects the more developmentally mature state of newborn lambs than humans and, therefore, a greater need for fetal energy substrate (166, 242, 421). To achieve high fetal fructose concentrations, the sheep placenta converts maternal glucose to fructose, which crosses into the fetal circulation. The fetal liver and other tissues then convert fructose to glucose-1 phosphate and glucose 6-phosphate, which provide energy substrate through the glycolytic pathway and citric acid cycle. In addition, fructose may further promote fetal growth via activation of the mammalian target of rapamycin signaling pathway (242). Fetal fructose does not cycle back to the maternal circulation, and thus the sheep fetus acquires and retains energy from its mother to expedite growth and maturation. Although fructose concentrations are lower in the human than sheep fetus, the polyol pathway that synthesizes fructose is highly active in early human pregnancy, leading to higher polyol and fructose concentrations in fetal coelomic and amniotic cavities than in maternal serum, and may be an adaptation to the low-O_2 environment (215). Additionally, in both sheep and human placentas the aldose reductase pathways (the first step in fructose and polyol synthesis) are highly active. Thus, in human and sheep gestation, fetal fructose concentrations are higher than maternal fructose concentrations.

Sheep and human placentas share similarities in amino acid transport and in the substantial metabolism of several amino acids (72, 193, 355, 379, 429). Stable isotope methods have been used to investigate transplacental flux of essential amino acids in pregnant ewes (354) and in humans (139), and in both species there is net fetal uptake of essential and nonessential amino acids (193, 354). In addition, these studies have highlighted that amino acid uptake appears able to occur against concentration gradients, with higher fetal than maternal concentrations for several amino acids, including in IUGR pregnancies of both species (379). The fetoplacental unit of sheep and humans also metabolizes and produces specific amino acids such as glycine and glutamine, which are released into the maternal circulation, and metabolites such as ketoisocaproic acid (193, 306). In humans, uptake of amino acids from the maternal circulation into the placenta involves many transport systems; the best studied of these are the Na-dependent neutral amino acid transporter system (system A) and the Na-independent neutral amino acid transporter system (system L), the latter of which is critical for essential amino acid uptake. Transport from the trophoblast to the fetus is less well studied, but it is understood to be predominantly via molecules such as system A in conjunction with system L transporters (439). The expression patterns of specific transport systems have not been as clearly defined in the sheep as in the human placenta, although various transporter system types have been investigated using nonmetabolizable amino acids with different affinities for different amino acid transport systems. Results of these studies in sheep suggest that, consistent with the human, neutral amino acids are taken up into the placenta from the uterine circulation by transporters displaying characteristics

similar to system A and essential amino acid uptake is via transporters displaying properties to similar to system L (94, 224).

Transfer of fatty acids across the human placenta is complex. In human placenta, lipases on the maternal-facing syncytiotrophoblast membrane release nonesterified fatty acids (NEFAs) from lipoproteins to allow their uptake down a concentration gradient into the syncytiotrophoblast by multiple fatty acid transporters. NEFAs are bound to intracellular fatty acid-binding proteins (FABPs) within the syncytiotrophoblast and then transferred to the fetal circulation via fatty acid transporters expressed on the fetal-facing syncytiotrophoblast membranes (248). The fatty acid transporter family members *SLC27A1–4* and *6* are expressed in the human placenta, and the SCL27A1 protein has been localized to both maternal- and fetal-facing membranes. The human placenta also expresses placenta-specific membrane-bound FABP (FABPpm) on the maternal-facing membrane only, which is likely important for transport of long-chain polyunsaturated fatty acids into the placenta and fatty acid translocase (CD36). Potentially, NEFAs may also cross the placenta by simple diffusion, although the contribution of this process is unclear. The ovine placenta also expresses lipoprotein lipase, as well as the fatty acid transporters SCL27A1, SCL27A4, CD36, and FABPpm (284, 481). Consistent with the localization pattern in the human placenta, SLC27A1 is localized to both maternal- and fetal-facing membranes of ovine trophoblasts (481). Fetal uptake of fatty acids is thought to be much lower in sheep than humans, given the lack of difference between umbilical arterial and venous concentrations of free fatty acids in normal ovine pregnancies (297). Somewhat in contradiction to this hypothesis, however, maternal human obesity upregulates placental *SCL27A1*, *SCL27A4*, and *CD36* expression and increases fetal circulating NEFA concentrations (481). Placental expression of lipoprotein lipase, transporters (*SCL27A4* and *CD36*), and FABPpm also increases in undernourished ewes, suggesting that fatty acid transport to the fetus is physiologically important (284).

In summary, the sheep and the human placenta display similar concurrent perfusion properties and transplacental O_2 and glucose characteristics, consumption, and metabolism, although full characterization and species differences in aspects of amino acid and fatty acid transport and metabolism require deeper investigations. All these features are critical to facilitation of normal fetal development and growth. However, these demonstrated similarities between the two species highlight the importance and utility of the sheep placenta as a model for aspects of human placental function and metabolism.

Fact 11: Sheep Are an Important Model of Glucose Metabolism During Pregnancy and the Programming Effects of an Adverse Uterine Environment on Glucose Metabolism in the Offspring

The fact that adult sheep have a metabolism largely fueled by short-chain fatty acids is often used as an argument for limitations in the use of this species as a model for human pregnancy. What is not well understood is that, under normal circumstances, only very small amounts of fatty acids cross the ovine placenta (116). Like the human conceptus, the sheep fetus and placenta depend on glucose as the main substrate, along with amino acids, for growth (28). After the first few days of postnatal life, nearly all the glucose that enters the reticulorumen (via ingestion of maternal milk) is metabolized quickly by the microbial flora. Pregnancy in the sheep, therefore, requires maternal glucose production by gluconeogenesis and effective transport across the placenta. One of the main products of rumen microbial fermentation, propionate, is the preferential substrate for gluconeogenesis, but ewes are also well equipped to produce glucose from glycerol, ketones, and amino acids (329). During pregnancy, ewes develop pregnancy-related insulin resistance (214, 363), which also occurs in humans and rodents (254, 363). This generates a concentration gradient of glucose that favors transplacental glucose transport by facilitated diffusion and placental glucose transporters that are common to sheep and humans (31, 115, 177, 207, 411). One difference between sheep and human fetuses relates to the higher level of circulating fructose in the former, which may be due to a specific metabolic adaptation of the ruminant placenta (197).

The fetal sheep pancreas is increasingly glucose-sensitive as pregnancy proceeds (10, 129, 345), and the elegant fetal pancreatectomy experiments of Fowden et al. (133) demonstrated the clear importance of the glucose-insulin axis in ovine fetal growth. The importance of glucose metabolism in sheep during pregnancy (and lactation) strongly supports the argument that this species provides a more-than-useful paradigm for the study of metabolism during human pregnancy.

Studies have been performed in sheep to test glucose tolerance via a glucose clamp and to determine the expression of genes and molecules involved in insulin signaling in fat, muscle, and liver samples in both the mother and fetus (259, 263, 350). Furthermore, the placental transfer capacity of glucose can be studied in vivo, and the expression of glucose transporters can be determined in the placenta. For example, compared with control fetuses, the placentally restricted fetus has lower placental glucose turnover (349), lower plasma glucose concentration (324), and decreased *GLUT4* expression in skeletal muscle (324), associated with impaired insulin secretion, but normal whole body insulin sensitivity (350). By 1 mo postnatal age, the low-birth-weight lamb exhibits whole body insulin resistance, with gene expression changes suggesting that skeletal muscle, but not liver, is a major site of insulin resistance (89). Impaired insulin secretion relative to insulin sensitivity occurs from early postnatal life to adulthood, particularly in males (143). These studies reinforce the utility of the sheep in postnatal metabolic studies, particularly studies of developmental programming, where the similar developmental timing in sheep and humans means that events during pregnancy impact similar developmental stages in the fetus.

Fact 12: Sheep Are a Good Model to Investigate the Causes and Consequences of Preterm Birth

There is clear evidence from clinical studies that a complex interaction of socioeconomic, genetic, lifestyle, environmental, and disease factors underpin a woman's risk of preterm delivery. Accordingly, any discussion of a particular model's relevance to the study of preterm labor must be framed with reference to preterm labor as a complex syndrome.

With regard to the sheep model of pregnancy, much of its utility in advancing our understanding of prematurity relates to studies focused on those preterm deliveries associated with

abnormal intrauterine inflammation, which is commonly identified in association with infection of the fetus and gestational tissues (5, 153, 387). Accordingly, the sheep model of pregnancy has been put to excellent use by a number of groups in the development of interventions aimed at either preventing preterm birth or alleviating the impact of prematurity on gestational tissues and the neonate (106, 162, 204, 230, 322, 323).

In contrast to rodent (125, 384) and nonhuman primate (159, 160, 391) model systems, the introduction of florid intrauterine infection and inflammation in the pregnant sheep does not initiate preterm labor as long as the fetus remains viable (288, 413). This is clearly a departure from clinical observations in humans of increased risk of preterm labor associated with elevation of amniotic fluid and/or cord blood plasma cytokines or the presence of chorioamnionitis/funisitis (155–157, 388). Rather than being a hindrance to studying preterm birth, a number of groups have put this unique feature of the sheep pregnancy to excellent use in studying the impact of both acute (234, 338) and chronic (244, 245) inflammation on the fetus, changes in microbial populations in utero (85), and the ability of experimental therapies to resolve infection (21, 232, 302) and inflammation (208). Given its ability to tolerate surgical instrumentation, the sheep fetus has proven to be a useful model on which to perform compartmental analyses on the origins and progression of intrauterine inflammation and fetal inflammation deriving from the microbial agonist in the uterine environment (231, 244, 468, 469). From a mechanistic perspective, experiments conducted with pregnant sheep have also proven useful in understanding the role of key inflammatory agents, including interleukin-1, interleukin-8, and tumor necrosis factor-α, in the initiation and propagation of fetal inflammation and tissue injury (39, 204, 225, 326, 466). Lastly, in keeping with the increased appreciation for the importance of microbial diversity in influencing pregnancy outcomes (220), a number of investigators have used the sheep model of pregnancy to investigate changes induced by microorganisms, notably *Ureaplasma parvum* (189, 230) and *Candida albicans* (288, 347), in fetal lung maturation and tissue inflammation.

Despite profound resistance to entering preterm labor in response to intrauterine inflammation and/or infection, the sheep model of pregnancy is clearly an important tool for understanding the pathophysiology of infection-associated preterm birth. Moreover, the sheep model of pregnancy offers an excellent model system for the design and testing of novel antimicrobial and anti-inflammatory interventions. Also, because lambs can be reared for long-term studies, they are a useful system to assess both the acute (i.e., perinatal) and long-term outcomes of preterm birth, antenatal infection, and treatments.

Sheep have recently been used to study the effects of preterm birth on offspring development. Vaginal delivery can be induced prematurely using drugs (such as epostane) that inhibit progesterone synthesis, together with clinically relevant doses of corticosteroids to stimulate lung maturation (90). With use of such methods, lambs can be delivered vaginally as early as 0.8 full term and raised to adulthood (335). Few other laboratory species can survive preterm birth and be raised to maturity. Studies on the effects of preterm birth in sheep have been aimed at understanding the effects of early birth per se on lung (92, 407), kidney (417), and heart and major artery (36, 91) development.

CONCLUSIONS

The aim of this review was to highlight the advances in perinatal human medicine following translation of research using the pregnant sheep, its fetus, and offspring. Despite differences between the species, the similarities in the timing of critical organ development in relation to birth between humans and sheep are particularly valuable for translation. Many questions around fetal development and the risk-to-benefit ratio of pregnancy interventions aimed at improving outcomes throughout life for mothers and their babies remain to be answered, and sheep models of pregnancy complications are better suited than commonly used laboratory species to undertake these investigations.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

J.L.M. and M.J.B. conceived and designed research; J.L.M. prepared figures; J.L.M., M.J.B., K.J.B., J.R.D., M.G.F., K.L.G., D.A.G., C.L.G., R.H., E.A.H., M.W.K., M.C.L., T.J.M., G.C.M., M.H.O., T.R.R., C.T.R., J.Y.S., and R.L.T. drafted manuscript; J.L.M., M.J.B., K.J.B., J.R.D., M.G.F., K.L.G., D.A.G., C.L.G., R.H., E.A.H., M.W.K., M.C.L., I.C.M., T.J.M., G.C.M., M.H.O., T.R.R., C.T.R., J.Y.S., and R.L.T. edited and revised manuscript; J.L.M., M.J.B., K.J.B., J.R.D., M.G.F., K.L.G., D.A.G., C.L.G., R.H., E.A.H., M.W.K., M.C.L., I.C.M., T.J.M., G.C.M., M.H.O., T.R.R., C.T.R., J.Y.S., and R.L.T. approved final version of manuscript.

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