Equine Fetal Growth and Development

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ABSTRACT: If adversely affected, maternal, uteroplacental, and fetal factors could lead to intrauterine growth retardation (IUGR) in humans and animals. Ultrasonographic examination of high-risk pregnancies to evaluate fetal well-being (i.e., equine biophysical profile) and growth and development (i.e., anthropomorphic parameters) is a new technique in equine veterinary medicine. Reference anthropomorphic parameters, as in human populations, must be established to diagnose IUGR in an equine fetus. Accurately assessing a high-risk pregnancy is crucial because there is a high probability that the mare and foal will need veterinary assistance. In addition, high-risk pregnancy results in high perinatal mortality and morbidity as well as deleterious effects later in life.

Fetal ultrasonography has been used in human obstetrics for the past 30 years. Today, the principal applications in human obstetrics include the following:*

1. Estimating fetal age when the menstrual date is not known
2. Evaluating fetal growth and development (i.e., anthropomorphic measurements)
3. Evaluating fetal well-being (i.e., biophysical profile)

Several parameters can be measured to estimate fetal age based on the stage of gestation. In humans, fetal growth standards have been determined for various reference populations from various locations. Based on these standards, human perinatologists are able to diagnose intrauterine growth retardation (IUGR; i.e., “small for gestational age”) in fetuses, which are a high-risk population.2 Low birth weight (i.e., IUGR) and birth weight that is low for gestational age are

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associated with increased perinatal morbidity and mortality as well as various cardiovascular and metabolic diseases later in life.3–5

In horses, perinatal ultrasonography is a relatively new technique. A significant difference from human obstetrics is that the precise date of conception is usually known in horses.6,7 Thus the most important uses of this technique are as follows:

- Evaluating fetal growth and development to identify IUGR
- Evaluating fetal well-being
- Creating accurate growth charts for the equine population

Several parameters can be measured ultrasonographically to assess fetal growth and development in the equine fetus. Five of the most important parameters are biparietal diameter, eye volume, thoracic diameter, aortic diameter, and femur length.

This article defines growth and development, discusses the parameters that affect them, and addresses the importance of assessing fetal growth in high-risk pregnancies.

GROWTH AND DEVELOPMENT

Fetal development is characterized by sequential patterns of tissue and organ growth, differentiation and maturation that are determined by maternal environment, uteroplacental function, and the inherent genetic growth potential of the fetus. If the circumstances are optimal, these factors will not have a rate-limiting effect on fetal growth and development. Thus the healthy fetus should achieve complete functional maturity and genetically determined somatic growth, and an uncomplicated delivery and a smooth neonatal cardiopulmonary and metabolic adaptation to the extrauterine life can be anticipated.2

Growth signifies an increase in fetal size. The factors contributing to this increase are highly complex because changes in cell numbers, cell size, and intracellular fluids are all involved and make separate contributions to the patterns and timing of growth in different organs and tissues as gestation advances.8

Fetal growth can be divided into two phases:

- In the hyperplastic phase, fetal tissues and organs primarily increase in cell number. This occurs during embryonic and early fetal growth.
- In the mixed hyperplastic and hypertrophic phase, cell size increases along with cell number during the later part of fetal life.

Fetal growth is an important concept because the outcome will be different depending on whether the fetus is affected in early or late intrauterine life.

In the human fetus, if fetal growth is measured as fetal weight gain (i.e., grams per day), fetal growth is constant during the second trimester, accelerates during most of the third trimester, but declines near term, which is thought to be related to some undefined restraint factors, possibly uterine size or placental function. During the neonatal period, the rate of weight gain accelerates again.

In the equine fetus, fetal weight gain (i.e., growth) increases linearly from day 200 of gestation until foaling and is linearly related to placental weight and surface area.8,9 It has been shown that equine fetal growth is directly affected by growth of the allantochorion and that the total microscopic area of fetomaternal contact is affected by maternal and fetal genotypes.5

Occasionally, fetal growth and development occur under abnormal intrauterine conditions. Terms for foals subjected to abnormal maternal, placental, and/or fetal circumstances that restrained growth include IUGR, dysmature, or postmature. Although dysmature was often used in the past, IUGR is considered to be more descriptive.

IUGR has been defined as a deviation from, or a reduction in, an expected fetal growth pattern and is caused by multiple adverse effects on the fetus that inhibit its normal growth potential.2 Foals affected by IUGR are a high-risk group because of cumulative adverse effects on intrauterine survival, delivery, and neonatal adaptation that could affect foals later in life.7

In humans, IUGR is a major cause of perinatal mortality and postnatal morbidity.10,11 It has been recognized that the relationship between IUGR and conditions later in life are particularly relevant to horses with the primary purpose of athletic performance.12

Fetal adaptations to an adverse uterine environment, of which low birth weight is the most obvious marker, may permanently damage the structure, physiology, or regulatory functions of organs, leading to pathologic effects in adulthood.4,12,13

IUGR DETERMINANTS

If affected, maternal, uteroplacental, and fetal factors could lead to IUGR.

Maternal Factors

Physical Environment and Inheritance

In horses, paternal genes that control size exert relatively little influence on the fetus and are expressed mainly in postnatal life. Maternal genetic contribution is confounded with nongenetic maternal effects.8 The
correlation between body (i.e., uterine) size and foal size has been shown by the classical experiments of Walton and Hammond and confirmed by Allen et al. These experiments illustrate that birth size reflects maternal size and the constraints imposed by the maternal uterine environment. They also show that postnatal growth rate is affected by the mare's size. Small mothers produce smaller offspring than large mothers.

In all species, fetal growth declines as the number of fetuses increases. Uterine restraint factors limit fetal growth in twin pregnancies. Placental insufficiency (the main cause of fetal growth retardation in equine twins), vascular anastomoses, and nutritional factors also interfere with fetal growth in these pregnancies.

**Maternal Nutrition**

In human pregnancy, maternal weight and pregnancy weight gain are two important independent variables that affect fetal growth. Underweight or malnourished mothers deliver infants with diminished birth weights. Maternal nutrition is important beginning at the embryonic stage because it affects the maternal endocrine environment required for maintaining early pregnancy. Recent studies indicate that disturbances in micronutrients during early fetal life could have adverse effects, such as fetal malformation. Restriction (either total or protein) of maternal dietary intake in sheep and rats causes IUGR and metabolic disturbances in postnatal life.

In horses, nutrition is also very important beginning with the early stages of gestation. Enteropathies, such as malabsorption syndrome, decrease the uptake of essential nutrients for the fetus. Interestingly, this syndrome does not always cause IUGR but may have long-term effects on postnatal life. Poor maternal nutrition can reduce uterine blood flow, placental transport, villous area, and placental weight, thereby affecting normal fetal growth and development.

The timing of nutrient insult plays a major role in fetal outcome. If nutrient supply is restricted acutely, fetoplacental functioning may be maintained in the short term by consuming endogenous fuels. If the insult is chronic, however, reduced substrate consumption is the only adaptation possible, resulting in IUGR or postnatal effects. IUGR is not always reversible postnata lly once nutritional restriction is relieved.

Hormones such as insulin, thyroxine, cortisol, and prostaglandins are essential for adapting fetal growth and metabolism to the existing intrauterine environment and ensure the survival of the fetus and mother during nutrient deprivation. However, this adaptation may have deleterious effects later in life.

**Chronic Disease**

Of all the disease mechanisms that interfere with fetal growth, those resulting in uterine hypoxia and/or ischemia have the most extreme effect on fetal growth.

In humans, pregnancy-induced hypertension is a major concern to the perinatologist because of its adverse effects on uteroplacental perfusion, fetal growth, and well-being. Another major factor associated with alteration of fetal growth is maternal hypoxemia.

In equine perinatology, maternal hypoxemia has a considerable impact on fetal growth. Severe maternal illness accompanied by anemia, hypoproteinemia, and endotoxemia adversely affects uteroplacental blood flow. Also, postterm pregnancies have been associated with placental insufficiency and IUGR. Age-related changes in the uterine arteries could play a role in the development of endometritis, thus altering perfusion in the maternal microcotyledons.

Signs of IUGR in foals have been associated with small placentas, placentitis, placental separation, postterm pregnancies, advanced maternal age, hydrops allantoids, and twins.

**Drugs or Toxic Agents**

**Cyanide.** Cyanide has a direct effect on growth by binding to cytochrome oxidase to form a very stable cyanide–cytochrome oxidase complex, thus stopping the chain of cellular respiration. Consequently, hemoglobin cannot release oxygen to the electron transport system, resulting in cellular hypoxia. The endpoint of this pathophysiologic mechanism is diminishing oxygen delivery from mother to fetus and from the fetus to its tissues.

**Fescue Toxicosis.** The ergot alkaloid, produced by the fescue endophyte, affects the fetal hypothalamus, thus ultimately affecting the secretion of T3 and cortisol. Adrenocorticotropic hormone, cortisol, and T3 levels are significantly lower in foals of mares affected by fescue toxicity. The fescue endophyte also suppresses fetal adrenal gland activity, further contributing to the low concentration of cortisol. Cortisol is important for lung development, surfactant production, hepatic glycogen deposition, and changes in gastrointestinal structure and function.

Low fetal plasma concentration of cortisol and T3 are associated with prematurity. Activation of the hypothalamus–pituitary–adrenal axis in the equine fetus, which occurs very late in gestation, is important for increasing the activity of the hypothalamus–pituitary–thyroid axis. Low concentrations of thyroid hormones at parturition contribute to the anomalies in energy metabolism and behavior observed in premature foals.

**Corticosteroids.** Continuous infusion of hydrocorti-
of amino acids; synthesis of peptides, steroids, growth factors, and cytokines; and support of placental maturation and growth.

The placenta has the capacity to control fetal growth. Placental growth factors match the rate of fetal growth according to the available substrate supply.

Placental size and fetal size are directly related. Experiments in sheep showed that reducing placental size by uterine carunculectomy before pregnancy results in smaller fetuses.

In mares, there is a significant uptake of oxygen and glucose by uteroplacental tissues during the second half of gestation. This is partly due to the continuous growth and structural remodeling of the equine placenta throughout gestation. In mares, cortisol does not cross the placenta (epitheliochorial placenta); thus administering synthetic glucocorticoids does not affect the fetus.

Phenylephrine HCL. An α-adrenergic sympathomimetic amine can constrict the uterine blood vessels, causing uterine hypoxia and/or ischemia. There are several reports in the human literature about the teratogenic effects of sympathomimetic drugs. They are difficult to extrapolate to horses because of the marked difference in placental structure between humans and horses.

Gentamicin. Gentamicin administered at 6.6 mg/kg/day to mares in late gestation was not detected in postpartum foals, indicating that the drug does not cross the equine placenta. Because toxic effects on the fetus are unlikely, it is not necessary to modify the dosage of gentamicin when a mare becomes pregnant. In other species, gentamicin crosses the placenta, and fetal concentrations range from 15% to 50% of those found in maternal serum.

Optimal fetal growth depends on efficient function of the placenta as a nutrient supply line, for gaseous exchange and waste (fetal creatinine) removal, and for fetal protection from a maternal immune response. The placenta requires a large amount of energy to maintain fetal growth-promoting roles, including active transport of amino acids; synthesis of peptides, steroids, growth factors, and cytokines; and support of placental maturation and growth.

Placental insufficiency means that the placenta fails as a respiratory, nutritive, and/or endocrine organ, leading to IUGR. Conditions leading to IUGR and in which the main pathologic mechanism is placental insufficiency include chronic placentitis, partial chronic placental separation, underweight placenta, postterm pregnancies, advanced maternal age, twin pregnancy, and fescue toxicosis.
In cases in which the maternal blood supply is moderately affected or there is chronic maternal anemia and the hypoxic insult is mild, the placenta has the ability to undergo compensatory hypertrophy. The enlargement of the placenta is an attempt to increase the surface area available for transfer of oxygen and nutrients to the fetus. When this happens, neonates are smaller because of IUGR. In humans, hypertrophy of the placenta is associated with high morbidity. When the maternal blood supply is more severely impaired, the placenta cannot respond by hypertrophy. In this case, both the fetus and placenta are small.

Allen et al conducted an experiment in which thoroughbred-in-thoroughbred and pony-in-pony pregnancies were used as controls to study pony-in-thoroughbred (luxurious in utero environment) and thoroughbred-in-pony (deprived in utero environment) pregnancies. The placental (allantochorion) growth was increased in the deprived pregnancies, but these foals experienced IUGR. This study showed the same results as human studies: When uterine conditions are adverse, the surface area of the placenta increases in an attempt to provide nutrients and oxygen to the fetus; however, there are deleterious consequences to fetal growth.

Fetal Factors
Optimal fetal growth depends on adequate provision of substrates, their effective placental transfer, and the regulatory factors that affect nutrient use by the fetus. Besides nutrients, oxygen must be transferred appropriately and a normal hormonal environment must be present. If everything is normal, the inherent growth potential of the fetus will be achieved.

Successful parturition in any species occurs only after the fetus is sufficiently mature to survive. Therefore, the mechanisms controlling the time of parturition are orchestrated with the timing of fetal development. In the equine fetus, in which final maturation occurs in the last 1% of the pregnancy, the timing for final development and parturition is especially critical.

ABNORMAL FETAL GROWTH PATTERNS
Fetal growth retardation caused by any of the factors already discussed can originate early (hyperplastic phase) or late (hypertrophic and hyperplastic phase) in fetal development. Reduced fetal growth early in gestation produces a symmetrically growth-retarded fetus: Head circumference, weight, and length are proportionally affected. Uteroplacental insufficiency and nutritional deficiency are the main factors that cause growth retardation later in gestation. If the placenta is compromised during this phase of the pregnancy, asymmetric IUGR will occur: The fetus experiences relatively normal head (and brain) growth resulting from preferential perfusion of the brain with well-oxygenated blood containing adequate substrates, but its body weight and somatic organs are seriously affected. The differentiation between symmetric and asymmetric growth retardation is important, at least in human perinatology, because fetuses with asymmetric growth retardation
have a worse outcome. There are currently no epidemiologic studies to evaluate the outcomes of symmetric and asymmetric fetal growth retardation in horses.

**EQUINE ANTHROPOMORPHIC PARAMETERS**

We recently completed a field study in which we evaluated five anthropomorphic parameters in 33 normal thoroughbred mares and recorded fetal and placental weights from normal deliveries. The parameters were measured via transabdominal ultrasonography during a 30-day interval, from day 130 of gestation until parturition. These measurements can be obtained with a 3.5-MHz curvilinear probe available on many ultrasound machines. The following parameters were assessed:

- Biparietal diameter (Figure 1)
- Eye volume (Figure 2)
- Aortic diameter (Figure 3)
- Thoracic diameter (Figure 4)
- Femur length (Figure 5)

Twenty-five mares finished the study, and data from their foals and placentas were recorded. The foals that finished the study were clinically healthy and have had a normal perinatal adaptation.

The parameters were analyzed statistically using regression and correlation analysis. Relationships between each of the five parameters and days of pregnancy were established. Correlations between some of the parameters and placental and foal weight were determined.

Growth charts can be constructed from successive ultrasonographic evaluations of normal mares (Figure 6). These charts are valuable for assessing fetal growth and development.

The data from this study will have several applications:

- Assessing fetal growth and development
- Follow up of high-risk pregnancies
- Using it in conjunction with the equine biophysical profile to more accurately assess problematic pregnancies
- Comparing it with data from previous studies in which normal and abnormal pregnancies were evaluated

**CONCLUSION**

The antenatal diagnosis of IUGR in equine fetuses is essential because intensive obstetric and neonatal management are required to improve the outcome of high-risk pregnancies. Detecting IUGR in equine fetuses to
evaluate their neonatal adaptation and athletic performance later in life will be important because this kind of data is currently lacking in equine medicine.

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REFERENCES
1. Which of the following statements regarding IUGR is true?
   a. There is no association between IUGR in a fetus and metabolic or cardiovascular problems later in life.
   b. IUGR can influence the athletic performance of horses.
   c. IUGR is a fetal adaptation to an adverse uterine environment, with no adverse effects occurring later in life.
   d. No association between IUGR and high mortality and morbidity has been shown in humans.
   e. Dysmature is a more descriptive term than IUGR.

2. Which three factors, if affected, could lead to IUGR?
   a. maternal, environmental, paternal
   b. placental, fetal, paternal
   c. maternal, fetal, environmental
   d. uterine, maternal, paternal
   e. maternal, uteroplacental, fetal

3. A fundamental difference in growth between equine and human fetuses is that
   a. equine fetal growth declines during the third trimester of gestation.
   b. equine fetal growth is linear from the third trimester of gestation until foaling.
   c. equine fetal growth is not correlated to placental weight.
   d. several factors slow equine fetal growth during the third trimester.
   e. an equine fetus is not affected by the growth of the allantochorion.

4. Which of the following characterizes the hyperplastic phase of fetal growth?
   a. The cell size in tissues and organs increases.
   b. It occurs during late gestation.
   c. An increase in cell number occurs during the last trimester of gestation.
   d. Cell number and size increase concurrently.
   e. The cell number in tissues and organs increases.

5. The administration of exogenous glucocorticoids does not have an effect on equine fetal maturation because
   a. corticoids do not play a major role in equine fetal maturation.
   b. maturation occurs late in gestation.
   c. corticoids inhibit the fetal pituitary–hypothalamus–adrenal axis.
   d. the equine placenta is epitheliochorial.
   e. corticosteroids are potentially toxic to the equine fetus.

6. Which of the following statements is true regarding the effects of chronic to mild chronic hypoxic–ischemic insults on fetal and placental growth?
   a. Mild chronic insults do not affect placental or fetal growth.
   b. The placenta and fetus are small.
   c. The equine placenta cannot respond to an insult by hypertrophy.
   d. The placenta has the capacity to undergo compensatory hypertrophy, and the fetus is larger than normal.
   e. The placenta has the capacity to undergo compensatory hypertrophy, even though the fetus is affected by IUGR.

7. If the fetus is affected during the hyperplastic phase of fetal growth, the foal’s
   a. growth will be retarded symmetrically.
   b. body will be larger than its head.
   c. growth will be retarded asymmetrically.
   d. head will be normally sized, but its body will be small.
   e. size will be normal because growth is not affected by insults early in fetal life.

8. Which of the following statements regarding asymmetrically growth-retarded foals is true?
   a. The head will be normal, but body weight and the somatic organs will be severely affected.
   b. The head is smaller than the body.
   c. The insult occurred during the hyperplastic phase of fetal growth.
   d. There is preferential perfusion to the somatic organs.
   e. Placental insufficiency does not play an important role in this process.

9. Which of the following statements about maternal nutrition is true?
   a. Poor maternal nutrition during the early stages of gestation does not affect fetal growth.
   b. Chronic malnutrition of the mare does not affect fetal growth.
   c. Maternal nutrition is very important, even during the early embryonic stages.
   d. Disturbances in micronutrients in humans does not influence fetal growth.
   e. Fetal adaptation to an adverse intrauterine environment does not produce any adverse effects later in life.

10. Which of the following statements regarding uteroplacental factors is true?
    a. Fetal and placental growth are not correlated in the equine species.
    b. The placenta has the capacity to control fetal growth.
    c. The placenta has the capacity to undergo hypertrophy if it is affected by an acute insult (e.g., acute maternal hemorrhage).
    d. In humans, placental hypertrophy is associated with beneficial postnatal effects.
    e. When uterine conditions are chronically adverse, the placental surface area decreases.