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Fetal death: comparative aspects in large domestic animals

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Abstract

Although the majority of pregnancy failures occur during the embryonic period, reports indicate that approximately 5% of detected pregnancies are lost during the fetal period, underlining the fact that fetal death is a substantial cause of economic loss. However, examination for fetal development or death during pregnancy is not performed routinely in domestic animals, and reference curves for normal fetal growth are, therefore, scarce. In this paper, the numerous possible causes of fetal death are reviewed briefly, with emphasis on the role of placental problems in fetal death and impaired fetal viability. In this respect, the role of placental insufficiency as a cause of pregnancy loss in twin pregnancies in monotocous species is well known, whereas the abnormal placental development leading to retarded fetal growth during pregnancies in recipients of in vitro produced (IVP) or nuclear transfer (NT) embryos has been less extensively documented.

Fetal viability or death can be evaluated using hormonal, chemical and ultrasonographic parameters. For example, the viability of the feto-placental unit can be examined by measuring maternal plasma concentrations of oestrone sulphate or the placental proteins, including pregnancy-associated glycoprotein (PAG) and pregnancy-specific protein B-60 (PSPB-60). Low concentrations of any of these three indicate either no pregnancy, or if pregnancy was confirmed earlier, fetal death and abnormally high or low levels can indicate fetal abnormality.

Ultrasound can be used to examine the fetal heart rate (FHR), the incidence of fetal movements (FM), the appearance of fetal fluids and the development of the fetus and placenta. However, although abnormal FHRs have been correlated to subsequent fetal death, it is important to remember that there is a large physiological variation in FHR at the end of gestation, due to different behavioural states and differences in FM patterns. Although monitoring fetal viability and death using hormonal and ultrasonographic evaluations is possible during pregnancy in domestic animals, there is considerable physiological variations in the ‘normal’ values. Therefore,-

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suitable combinations of tests need to be identified and more accurate reference values generated before such approaches can be considered reliable for monitoring the status of individual fetuses.

Keywords: Fetus; Death; Viability; Ultrasonography; Pregnancy-specific proteins; Placenta; Fetal heart rate; Ruminant; Pig; Horse

1. Introduction

Under field conditions, routine pregnancy diagnosis in cattle is performed at around day 40, i.e. at the onset of the fetal period (Noakes et al., 1996b). If the animal is pregnant, further interest in pregnancy diagnosis recedes until shortly before parturition, unless obvious signs of imminent fetal death or abortion are seen. Fetal loss rates of 5–6% between the time of pregnancy diagnosis and parturition are thought to be common in cattle (Baxter and Ward, 1997; Dunne et al., 2000), and it may reach 10% (Lopez-Gatius et al., 2002). In bovine pregnancies, resulting from the transfer of in vitro produced (IVP) embryos, higher embryonic and fetal loss rates have been reported (reviewed by Taverne et al., 2002). In one study comparing pregnancy losses in recipients of IVP embryos cultured under different conditions, fetal mortality rate with embryos cultured in cell co-culture system was 11.8% compared to the 8.5% in recipients of embryos cultured in synthetic oviduct fluid (SOF), and total returns to estrus were 51.6 and 46.1%, respectively, indicating higher than normal embryonic and fetal losses (van Wagtendonk-de Leeuw et al., 2000). Even higher rates of fetal loss (33–43%) have been reported in pregnancies derived from cloned embryos (Heyman et al., 2002).

Fetal losses in the mare after confirmation of pregnancy between days 35 and 40 has been reported to range from 5–25%, the latter data coming from a stud farm with a history of early fetal loss syndrome (Frymus et al., 1986; Morris and Allen, 2002; Morehead et al., 2002). Fetal losses in pigs are mostly represented by stillborn piglets and are reported to range from 3–12% (van der Lende et al., 2001, 2003; Lucia et al., 2002).

In the overall calculation of fetal loss, fetuses born dead or unusually weak neonates that die within hours after birth, after a pregnancy of normal duration, should also be taken into account. Although dystocia is a major cause of stillbirth (Meyer et al., 2001b), impaired fetal well-being at the end of gestation leading to decreased neonatal viability, or even fetal death shortly before the onset of parturition, cannot be ruled out.

Economic losses resulting from fetal death are substantial since they include not only the loss of offspring but also a prolonged “open” period for the dam leading to increased culling rates. Meyer et al. (2001b) estimated an increase in the costs of replacing dairy calves of $ 75.9 million during the period 1985–1996 as a result of an increase in the incidence of stillbirth from 9.5% in 1985 to 13.2% in 1996. This review will discuss placental problems as a cause of fetal death, together with the various means of de-

tecting fetal death, or, more importantly, threatened fetal death in domestic animal species.

2. Causes of fetal death

The causes of fetal death are manifold, but can be divided broadly into those of infectious and those of non-infectious origin. An overview of the most frequently detected infectious agents and the species that they affect is presented in Table 1. Some infectious agents cause fetal death in several species, while other pathogens are more host-specific, such as *Brucella* in the cow and equine herpes virus-1 (EHV 1) in the mare. Some important abortive agents are essentially environmental contaminants, e.g. *Escherichia coli* and *Streptococcus zooepidemicus*, which, by way of ascending bacterial placentitis, are the most common causes of fetal death, abortion and stillbirth in the mare (Giles et al., 1993; Acland, 1993; Smith et al., 2003) and account for 10–20% of fetal losses in this species (Giles et al., 1993; Hong et al., 1993; Smith et al., 2003).

Neospora caninum has recently been recognized as one of the most important infectious causes of abortion in cattle and an organism that can persist for a long time in a herd (Anderson et al., 2000; Dubey, 2003) with the infection rates reaching 90%. Neospora infection usually causes abortion of an autolysed fetus between 3 months and term, with the majority occurring after the 6th month of gestation (Dubey, 2003). In cattle, the main route of transmission is vertical (Bergeron et al., 2000; Dijkstra et al., 2002), although dogs also form an important source of infection (Wouda, 2000). *Neospora caninum* abortions have also been reported worldwide in sheep, goats, horses and deer (Buxton et al., 2002), and it is speculated that *Neospora* will become an increasingly important cause of fetal death in these species in the future.

In sheep and goats, *Chlamydia* (enzootic abortion), *Coxiella* (Q fever) and *Toxoplasma* infections are the most important causes of abortion (Noakes et al., 1996a; Moeller, 2001). In a naive flock infected with *Chlamydia*, up to one-third of the ewes may abort, whereas in a flock where infection is endemic, 5–10% of animals are usually affected (Noakes et al., 1996a).

The results of post-mortem (PM) examinations of aborted fetuses are often disappointing since in about 60% of cases, the cause of an abortion is not established (Kirkbridge, 1992; Moeller, 2001; Campero et al., 2003). However, it is always advisable to perform a PM or laboratory investigation, especially if the abortion turns out to be the first of a series rather than just an isolated incident. In general, an abortion rate of 2% in a sheep flock is accepted as normal.

Several of the infectious causes of fetal death and abortion are zoonotic, e.g. *Brucella*, *Listeria*, *Coxiella*, *Chlamydia* and coccidial-like *Toxoplasma gondii* (De Kruif, 1993). Aborting animals shed large quantities of infectious agents and pose considerable risk to humans in contact, including farmers, animal caretakers and veterinarians (Pospischil et al., 2002). In some cases, consumers may also be at risk; for example, *Coxiella burnetti*, responsible for Q-fever, can be excreted in the milk of aborting goats for up to 52 days (Arricau Bouvery et al., 2003). The possibility of a zoonotic agent infection as the cause of abortion is an additional impetus for performing a PM on the aborus.

Table 1
Frequently diagnosed infectious agents in cases of abortion or stillbirth in the important farm animal species

Bacteria	Host	Viruses	Host	Fungi	Host	Others	Host
Brucella	C, S, G, P, H	Bovine herpes virus-1 (IBR)	C	*Aspergillus*	C, S, P, E	*Neospora caninum*	C, S
Campylobacter (Vibrio)	C, G	Equine herpes virus-1 (EHV1)	E	*Mucor*	C, E	*Trichomonas fetus*	C
Arcanobacerium (Actinomyces)	C, P	Bovine viral diarrhoea (BVD)	C	*Candida*	C, E	*Toxoplasma gondii*	S, G, P, H
Leptospira	C, S, G, P, E, H	Border disease	S, G			*Chlamydia*	C, S, G, H
Listeria	C, S, G, H	Mycoviruses	C			*Mycoplasma*	C, S, G, P, E, H
Salmonella	C, S, G, P, E, H	Bluetongue	C, S, G			*Coxiella* (Q fever)	C, S, G
E. coli	C, S, G, P, E	Parvo virus	C, P			*Coccidia*	S, G
S. zooepidemicus	E	Suid herpisvirus 1	P			*Babesia*	C, E
Rhodococcus equi	E	PRRS (Lelystad virus)	P			*Trypanosomum equiperdum*	E
		Eqine viral arteritis (EVA)	E				

C: cattle, S: sheep, G: goat, P: pig, E: horse, H: human/zoonoses. Based on Knudtson and Kirkbridge (1992), De Kruif (1993), Kirkbridge (1993) and Vendrig (2000).

3. Non-infectious causes of fetal death

Non-infectious causes of fetal death or compromised fetal health include malnutrition, stress and maternal endocrine imbalance. It has been suggested that one of the main causes of stillbirth and perinatal weakness in calves born to heifers is retarded fetal development as a result of low maternal feed intake at the terminal stage of pregnancy, combined with the stress of being housed with a new group. Similarly, dairy cows with a poor body condition score (1 point) have been reported to be 2.4 times more likely to lose their pregnancy during the early fetal stage (Lopez-Gatius et al., 2002; Silke et al., 2002). Maternal illness is also generally accepted as a potential cause of fetal death and abortion due to fever and/or the release of inflammatory products like prostaglandins into the systemic circulation. For instance, pregnant cows suffering from mastitis have a higher rate of abortion (Risco et al., 1999). Other environmental factors can also contribute to pregnancy loss. For example, heat stress in sheep has been shown to lead to decreased uterine blood flow and reduced birth weight in lambs (Dreiling et al., 1991). The incidence and types of non-infectious causes of fetal compromise are likely to differ between regions and countries.

Sire effects on fetal loss and stillbirth have been reported in cattle (Meyer et al., 2001a; Lopez-Gatius et al., 2002; Kindahl et al., 2002a,b) and genetic differences between lines have been shown to affect the incidence of stillbirth in pigs (Leenhouwers et al., 2001). In general, genetic abnormalities are more likely to result in embryonic mortality, although some may lead to fetal loss or deformities that cause severe dystocia.

In veterinary medicine, placental dysfunction other than via placentitis is probably underestimated as a cause of fetal death or compromised fetal health. Perhaps, the best example of impaired placental function in domestic animals is seen in pregnant mares carrying twins, in which the total placental surface area is often too small for one or both of the twins to survive to term (Acland, 1993). In such cases, the affected fetus usually dies during gestation, while the surviving fetus is generally born smaller than normal. Where early pregnancy diagnosis and manual twin reduction are not practised, twinning remains a major non-infectious cause of fetal death in the mare. Allen et al. (2002) have recently demonstrated the critical influence of placental size on neonatal development in the horse by showing that the birth weight of the foal is primarily determined by the total microscopic surface area of the allantochorionic microvilli. Small foals with signs of intrauterine growth retardation were associated with a placenta with a low total microscopic area of fetomaternal contact. Other common placental or feto-placental disorders include umbilical cord disorders, such as occluding torsion and long cord/cervical pole ischaemia (Acland, 1993; Hong et al., 1993; Smith et al., 2003).

In cattle, placental dysfunction has probably been underestimated as a cause of fetal death or compromise. However, as in the mare, twin pregnancy in cattle is associated with a higher abortion rate (Kirkbridge, 1992; Lopez-Gatius et al., 2002; Sakaguchi et al., 2002) and a lower per calf placental weight (Echternkamp, 1992). Additionally, in Japanese black beef cattle, intrauterine growth retardation has been shown to be correlated with feto-placental dysfunction (Ogata et al., 1999), and in a Swedish study on bulls with high rates of stillbirth among their offspring, the stillborn calves were noted to have heavier placenta than normal calves (Kindahl et al., 2002a,b). Embryo culture also appears to dramatically affect placental function, and placenta from IVP calves shows a difference in the distribution of placentomal

size, with increased volume density of bi-nucleate cells at day 63 of pregnancy (responsible for producing pregnancy associated proteins) and are heavier at parturition than those from normal calves (Farin et al., 2000, 2001; Hill et al., 2000; Bertolini and Anderson, 2002; Taverne et al., 2002). Unfortunately, different research groups have produced conflicting data, possibly because of the different times at which the placentas were evaluated during pregnancy. For pregnancies derived from cloned embryos, large placentomes (Heyman et al., 2002) and an increased incidence of hydroallantios have been reported (reviewed by Taverne et al., 2002).

There are indications that placental insufficiency plays an important role in the incidence of fetal death in the pig as well. Porcine placental growth occurs in important phases: between day 20 and 60 and after day 110 (reviewed by Wilson and Ford, 2001), which also coincide with the period at which fetal mortality rates are also very high (Van der Lende and van Rens, 2003). A comparison of the Meishan breed of pigs, which produce large number of live born piglets, with the Large White breed, which produces smaller number of piglets, the Meishan was shown to have smaller placenta occupying less uterine space, but a more than compensatory increase in vascularization of the placenta from around day 100 of gestation (Ford, 1997).

4. Diagnosis of fetal death

In farm animals, a pregnancy check during the fetal period is usually made only in those cases in which there are doubts with regard to the as to whether the animal is still pregnant status of the animal, or when there are clear signs of threatened pregnancy loss. Due to the size of the fetus and dam, a physical evaluation of the entire conceptus during the latter stages of gestation is difficult. Invasive methods, such as ultrasound-guided allanto- or amniocentesis, or installation of catheters in the fetus or amniotic cavity to examine or monitor fetal viability, will not be discussed because their value in predicting fetal compromise or death is insufficient to outweigh the risk of inducing abortion by tearing fetal membranes or introducing bacteria; that is not however to say that these techniques are not useful in a research setting (LeBlanc, 1997; Taverne et al., 2002).

5. Clinical examination

According to most textbooks, the clinical examination of a pregnant animal during the latter two-thirds of gestation consists of *per rectum* and *per vaginam* examinations and abdominal palpation, depending on the size of the subject. Findings during a manual *per rectum* examination, like the volume of fetal fluids present and the size of uterus and fetal body parts, are essentially only indicative with regard to the normality of pregnancy. An excessive volume of fetal fluids can be palpated in cases of hydroallantois, while an absence of fetal fluids can be detected in the case of a dead, mummified fetus. It should be borne in mind that differences in uterine tone may occur during late pregnancy due to periods of myometrial activity – the so-called contractures. These contractures have been described in several domestic species, including sheep and cattle (Weijden et al., 1981; Janszen et al.,

1990); they last between 10 and 20 min and, in the cow, occur approximately once every 2 h. The slight increase in uterine tone caused by a contracture should not be confused with the dramatic increase in tone that accompanies fetal expulsion during abortion. The absence of fetal movements (FM) during a *per rectum* examination is not uncommon and need not be abnormal since, during late gestation, periods of fetal activity alternate with periods of quiescence.

A speculum or manual examination of the vaginal cavity will not usually provide much additional information about the pregnancy, unless purulent or sanguineous discharge, fetal membranes or fetal parts are visible in the cervix. In the latter case, abortion will inevitably follow shortly afterwards. Abdominal palpation can be used to diagnose pregnancy, but is fairly unreliable and provides little information on the status of the fetus, unless active fetal movements are felt. The diagnosis of fetal compromise or death is thus difficult to make in domestic animals when only a basic clinical examination is performed.

6. Hormonal/chemical monitoring

Several hormones and proteins produced by either the ovaries, placenta and/or the fetus are either necessary for, or indicate, the maintenance of pregnancy. However, progesterone is not a useful indicator of fetal compromise or death because progesterone concentrations tend to remain elevated until shortly before fetal expulsion, whereas fetal death may have occurred much earlier. For example, after inoculating mid-gestation cows with *Sarcocystis cruzi* or *Campylobacter fetus*, Baetz et al. (1980) did not record a decrease in progesterone concentrations until the time of abortion. Engeland et al. (1999) similarly reported normal progesterone concentrations in pregnant goats, despite the in utero death of one out of twin or triplet fetuses.

The feto-placental unit produces oestrone sulphate, and the presence of oestrogen receptors in caruncular stromal cells during pregnancy suggests that oestrogens may play a role in placental growth and function in cattle (Hoffmann and Schuler, 2002). This hypothesis is supported by the positive correlation between maternal plasma oestrone sulphate concentrations after day 195 of gestation, and neonatal viability, calf birth weight and placental weight (Zhang et al., 1999). Additionally, dams of weak, growth-retarded calves do not show the expected (Kindahl et al., 2002b) pre-partum increase in oestrogens (Ogata et al., 1999). Preliminary data in a study of pregnancies from a bull associated with a high percentage of stillborn calves showed low maternal plasma oestrone sulphate levels, smaller cotyledons and higher placental weight, compared to pregnancies fathered by a normal bull (Kindahl et al., 2002a,b). These authors suggested that impaired placental function led to the production of smaller, weaker calves. However, because of the large individual variations, individual plasma oestrone sulphate concentrations are not a reliable indicator of fetal well-being in the cow (Dobson et al., 1993). In the mare, declining concentrations of oestrogens before day 280 are related to fetal compromise; however, some mares show no decrease in oestrogen concentrations before aborting (Schott, 1993). Decreased levels of oestrone sulphate have also been correlated to fetal losses after day 70 of gestation in goats (Engeland et al., 1999).

In the cow, pregnancy-specific proteins (PSPs) and pregnancy-associated glycoprotein (PAG), both produced by the trophoblastic binucleate cells, have been studied extensively since the mid-1980s (Zoli et al., 1992; Beckers et al., 1998). As well as being useful for pregnancy diagnosis per se, PAG has proven helpful in the detection of embryonic and fetal mortality during pregnancy (Szenci et al., 2000, 2003). In several studies, the PSPB and PAG concentrations were found to have decreased before progesterone concentrations fell and the fetus was expelled, indicating that the feto-placental unit was malfunctioning or that the fetus was already dead (Engeland et al., 1999, 2000; Szenci et al., 2003). In goats, Zarrouk et al. (1999) were able to correlate the death of a fetus with a drop in PSPB concentrations, before the fetus was expelled. A drop in PAG concentrations some weeks or months prior to abortion has also been reported in cattle (Humblot, 2001), and Taverne et al. (2002) concluded that a combined analysis of progesterone and PAG concentrations was a useful way of detecting pregnancy failure during the first trimester of bovine pregnancy. Increases in placental protein levels can also indicate fetal abnormality and, for example, although plasma PSP60 levels for ongoing nuclear transfer (NT) pregnancies did not differ to those for IVP or MOET pregnancies, PSP60 levels on day 50 in NT recipients that subsequently lost their pregnancy between day 50 and 90 were significantly higher (Heyman et al., 2002). Cloned pregnancies that developed hydroallantois also had significantly elevated PSP60 levels. It can be speculated that these increased levels of PAG seen during IVP pregnancies result from an increased density of binucleate cells in their placenta (Farin et al., 2001), although binucleate cell density and maternal plasma PAG concentrations have not yet been determined in the same animals. Disappointingly, only dramatic progressive decreases in PAG concentrations can be used to predict fetal death because of large individual variations in maternal blood PAG concentrations (Szenci et al., 2000).

7. Ultrasonographic monitoring

During the fetal period, ultrasonographic evaluation of the pregnancy can be performed either trans-rectally or trans-abdominally. In both cattle and horses, the trans-rectal approach is preferred during the first 3 months of gestation. Thereafter, the pregnant uterus tends to drop deeper into the abdomen such that it is difficult to visualise all parts of the fetus (Reef et al., 1996; Bertolini et al., 2002; Breukelman et al., 2004). The trans-abdominal approach is, therefore, preferred during late gestation in cattle and horses, and at all stages in small ruminants and pigs (Cohen et al., 1997).

Fetal size can be evaluated by means of ultrasonographic measurement of various fetal body structures. Measurements commonly used include the crown rump length (CRL), biparietal diameter of the cranium (BPD), cross-section of the abdomen (CAU), aortic diameter (AD) and the dimensions of the eyeball. Indeed, multiple measurements of bovine fetal parts (CRL, CAU, BPD and eyeball) have been used to construct reference curves for normal growth (Kähn, 1994; Ginther, 1998), which can then be used to estimate gestation length in cows with an unknown service date or, conversely, to investigate the normality of fetal growth and development in pregnancies of known gestational stage. Debris should not be seen in fetal fluids during an ultrasound evaluation and, if imaged repeatedly, may be a sign of a compromised or dead fetus (Ginther, 1998).

In cattle, determination of the fetal heart rate (FHR) and reliable measurement of fetal dimensions is only possible after about days 35–40 of gestation. The normal bovine FHR follows a parabolic curve after first detection at around day 40, reaching a peak of 170–190 beats per min (bpm) at around day 60 (Curran et al., 1986; Ginther, 1998; Breukelman et al., 2004) and then declining steadily towards term. The differences in absolute FHR values seen between studies presumably reflect differences in breeds examined and technique implemented. A similar pattern in FHR changes during normal pregnancy in the horse has been described (Matsui et al., 1984). Recent monitoring of FHR in cattle has focused on determining whether it can be used to indicate abnormal development of fetuses derived from IVP embryos (Bertolini et al., 2002; Breukelman et al., 2004). Bertolini et al. (2002) reported a significantly higher FHR in bovine IVP fetuses than in MOET fetuses during days 37–93 of pregnancy. Moreover, because the IVP fetuses also showed growth retardation during this period of pregnancy, it was suggested that the elevated FHR was associated with the deviant growth. In our own studies, fetuses that died during gestation were retrospectively found to have had basal FHRs that differed from those that progressed to term (Breukelman, 2000; Breukelman et al., 2004). Similarly, human fetuses that subsequently die in utero have been reported to show heart rates that differ significantly from normal viable fetuses (Schats et al., 1990; Achiron et al., 1991).

7.1. Ultrasonographic monitoring during the late fetal period

At the end of pregnancy, the bovine or equine fetus is difficult to image because of its large size, ventral position in the abdomen and the limited depth of penetration of affordable ultrasound equipment. In pigs and small ruminants, the presence of more than one fetus can complicate identification, although Cohen et al. (1997) were able to reliably identify individual piglets in a sow using a system of gridlines drawn on the abdominal wall.

Ultrasonographic monitoring of the fetus and placenta using the criteria published by Adams-Brendemuehl and Pipers (1987) and Reef et al. (1996) has been recommended for mares nearing the end of gestation but considered to be at risk of abortion. During the evaluation of the late gestational fetus, a so-called biophysical profile score is made that encompasses the FHR, gross fetal movements, fetal aorta diameter, fetal fluid quality and the utero-placental unit. Using this profile, Reef et al. (1996) were able to identify “at risk” foals (with a low biophysical profile score) that were later born compromised or even dead. However, a good biophysical profile score did not guarantee a positive outcome. At present, it is also not clear to what extent the scores calculated for thoroughbred or light horse mares are applicable to other horse breeds. Comparable measurements for the late gestation bovine fetus are not yet available largely because it is difficult to image the fetus trans-abdominally (Ginther, 1998).

7.2. FHR and FM monitoring

In several species, including the horse (Adams-Brendemuehl and Pipers, 1987), cow (Kähn, 1994; Ginther, 1998; Breukelman et al., 2004) and pig (Cohen et al., 1997), the FHR of normal fetuses declines gradually as parturition approaches. One interesting aspect of FHR monitoring, however, is the huge variation in values, even within an individual

fetus. Short periods of tachycardia are common and considered normal, especially if they are correlated with FM (Adams-Brendemuehl and Pipers, 1987; Jonker et al., 1994; Cohen et al., 1997). On the other hand, in horses, persistent tachycardia is an ominous sign because it is usually related to fetal or placental infection, maternal fever or fetal anaemia (Adams-Brendemuehl and Pipers, 1987). By contrast, prolonged periods of tachycardia have been reported to coincide with periods of intense FM in normal bovine pregnancies (Jonker et al., 1994). At the other extreme, periods of bradycardia in equine fetuses have been attributed to fetal asphyxia (Adams-Brendemuehl and Pipers, 1987) and, in Angora goats, periods of low basal FHR have been described prior to late gestation abortion (Wentzel et al., 1974). In sheep inoculated with *Toxoplasma gondii*, the FHR first increased but then dropped dramatically before the fetus died (Ortego-Pacheco, 1993). Cohen et al. (1997) also described a porcine fetus with an abnormal FHR pattern, which was subsequently born dead with obvious ascites.

Accelerations in FHR are usually correlated with FM and should be considered a normal reaction to increased activity (Martin, 1986; Adams-Brendemuehl and Pipers, 1987; Jonker et al., 1994). Any evaluation of FHR has to take account of FM because they are responsible for a great part of the physiological variation in FHR. The need for care when interpreting FHR measurements can be illustrated using IVP calves which tend to have longer limbs and a higher incidence of flexural deformities (see Taverne et al., 2002), both of which may well influence patterns of FM and, therefore, FHR.

During continuous FHR recordings in both human and animal fetuses, further variation in FHR stems from alterations in the so-called "fetal behavioural state" (for review see Nijhuis, 1992). In short, fetal behavioural states are periods of differing neuronal and physical activity that develop during the last trimester of pregnancy and are essentially represented by interchanging periods of high and relatively low activity. Fetal behavioural states can usually be recognised in FHR patterns by the alternation between periods with high variation in FHR, including the so-called accelerations (temporal increases of the FHR) and the presence of FM, and periods with low variation in FHR and a low incidence of FM. FHR accelerations seen during periods of fetal activity and periods of high variation in FHR are considered reassuring signs of fetal reactivity and well-being, whereas their absence over a prolonged period of time may indicate fetal compromise (Dawes, 1991). Variations in the baseline FHR are usually related to alterations in behavioural state and, in human fetuses, a regular change of behavioural states is considered a sign of a healthy fetus and is apparent as early as 28 weeks into pregnancy (Dawes, 1991). For this reason, if FHR is to be used as an indicator of fetal well-being, it is advisable to monitor continuously for a prolonged period and, preferably, in combination with FM recordings.

During the last month of gestation in both the cow (Jonker et al., 1998) and the pig (Cohen et al., 1997), it is possible to perform continuous, trans-cutaneous doppler FHR recordings (see Fig. 1). The computerised analysis of such antepartum doppler derived FHR measurements can then be performed using the Dawes system described for human FHR analysis, but based on data obtained from sheep fetuses (Dawes, 1991). In this system, the baseline FHR, the so-called short-term and long-term FHR variation, the occurrence of accelerations and decelerations and the incidence of FM are measured. In this way, in both the cow and the pig, alternating periods with high and low variation in FHR have been observed, suggesting the existence of fetal behavioural states in these species (Jonker et al.,

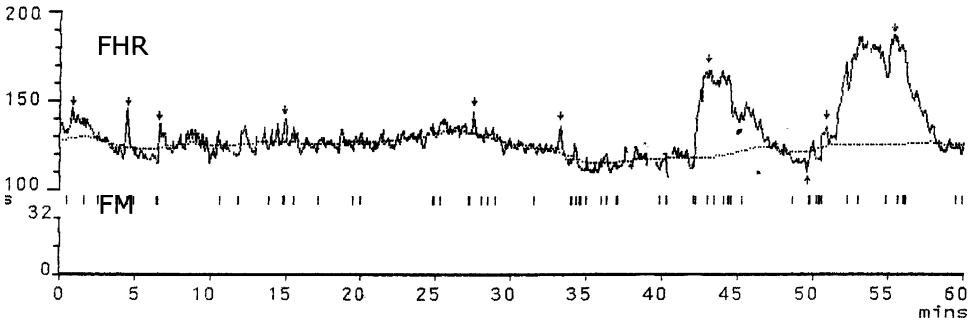

Fig. 1. A 1-h long trans-abdominal Doppler FHR recording performed 20 days before the birth of a normal healthy calf. During the first half hour, the baseline FHR was 122 bpm. Accelerations in FHR are indicated with a ↓. A clear difference in the scale of the variations in FHR is seen between the first 15 min and the following 15 min. During the last 30 min, the elevated FHR (tachycardia) was associated with an increased incidence of FM. Subsequently, the FHR returned to normal levels.

1994, 1998; Cohen et al., 1997). However, before computer analysed doppler antepartum FHR recordings can be used on a routine basis to evaluate individual cases, for instance, in the event of threatened abortion or in herds with an increased rate of stillbirth, reliable reference values need to be generated.

7.3. Fetal fluids and placenta

Equine fetal fluids should have a clear anechogenic appearance, although late in gestation some debris may be detected, particularly in the amniotic fluid (Renaudin et al., 1997; Renaudin et al., 1999a). However, if considerable debris is detected in the fetal fluids on several occasions, it may be an ominous sign. Conversely, changes in the echogenicity of the fetal fluids are often not observed even in known cases of placentitis (Renaudin et al., 1999b).

Ultrasonographic evaluation of the placenta has proven a valuable tool in the evaluation of suspected equine placentitis. It can be performed trans-abdominally or trans-rectally, where the latter approach is preferred because the transducer can be brought closer to the placenta and because it is more practical under field conditions (Renaudin et al., 1999a). The combined thickness of the uterus and the placenta (CTUP) is measured at the level of the cervical–placental junction during a trans-rectal examination, or at a place where no fetal parts are in contact with the placenta, if it is performed trans-abdominally. In general, the CTUP is relatively constant until the 8th month of pregnancy, after which it increases linearly towards term. In cases of placentitis, a premature or exaggerated increase in CTUP is often seen, and in some cases, early placental separation can also be detected (Renaudin et al., 1999b).

In sheep, ultrasonography proved a useful tool for studying the pathological processes that occur in the fetus and placenta after experimental infection with *Chlamydia psittaci*. Placental changes consisted of an alteration in the structure of the placentomes, which lost their normal round or oval shape and became more irregular in form. This change was detectable before fetal loss occurred, enabling early identification of affected ewes

(Ortego-Pacheco, 1993). Post-mortem examination confirmed necrosis of the cotyledonary part of the placentomes. To date, ultrasonographic evaluation of the placentomes in the cow has been restricted to the investigation of their size and thickness (Bertolini et al., 2002).

8. Conclusions

Fetal death and reduced fetal viability have numerous possible causes, but the actual cause in an individual case is often elusive. Nevertheless, there are several techniques for identifying dead or compromised fetuses. Feto-placental or fetal hormones or proteins, such as oestrone sulphate, PAG1 or PSP60, allow investigation of fetal viability via maternal serological examination, whereas biophysical monitoring can be performed by analysing FHR, FM and ultrasonographic aspects of the fetal fluids and placenta. At present, it is not entirely clear if altered concentrations of oestrone sulphate, PAG and PSP60 result from abnormal fetal development per se or altered placental function induced by abnormal fetal development. Ideally, hormonal and biophysical evaluations should not be seen as independent means of examining fetal development, but as complementary, and they are almost certainly interdependent.

For pragmatic reasons, the application of such techniques in veterinary practice will probably be limited to valuable animals or fetuses. Indeed, some of the techniques are already used in specialised equine clinics to monitor pregnancies thought to be at risk. Although the state of the techniques is promising, care has to be taken not to overestimate their current utility; most have yet to be properly validated for domestic animals and reliable reference values may not be available. In addition, even if a fetus is considered at risk, the treatment options are limited and the results of intervention often disappointing.

At a herd level, fetal monitoring could be used to study differences in the incidence of abortion or stillbirth between herds, even if a clinical intervention at the individual level is not the primary goal. Instead, the results might provide insight into the underlying causes and patho-physiological mechanisms of fetal death or poor viability, and thereby indicate possible adaptations to the breeding or management program.

In a research context, fetal monitoring is a valuable tool for investigating physiological and patho-physiological events during pregnancy, and will undoubtedly help improve our understanding of the mechanisms of fetal death and decreased fetal viability.

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