



Review article

Stress effects on the regulation of parturition in different domestic animal species

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ABSTRACT

This review summarizes current knowledge on stress-like responses in parturient animals and their role for the onset and fine-tuning of parturition. The antepartum maternal cortisol increase is part of the endocrine changes that initiate parturition but a further increase in cortisol release during labor indicates a stress response. During the last minutes of delivery, sinus arrhythmias occur in 80% of foaling mares and 60% of calving cows. Expulsion of the neonate is thus characterized by parasympathetic dominance. In late-pregnant cows transported by road, cortisol concentrations increased but relations between transport stress and abortion remain unclear. In mares, transport not only elicited a stress response but also advanced the time of foaling. Transferring parturient rats, mice and pigs after birth of the first pup or piglet, respectively, to a stressful environment prolonged the time until delivery of the next littermate. In rats and pigs, this was caused by an increased opioidergic tone that restrained oxytocin release. In mice, a stress-induced delay of subsequent deliveries was caused by increased sympathoadrenal activity. When foaling mares were transferred to an uncomfortable stable at fetal membrane rupture, time until complete birth of the foal was doubled. As in mice, increased sympathetic activity was the mechanism delaying the progress of foaling. An increased sympathetic activity is also present in parturient cows disturbed during an early stage of calving. In equine and bovine neonates, the immediate postnatal period is characterised by high sympathetic activity and an increase in cortisol concentration, indicating a pronounced stress-like response.

1. Introduction

Parturition is often suggested as one of the most stressful events in life, both for the dam and the newborn (Padbury et al., 1988; Mainau and Manteca, 2011). In a survey in the UK, veterinarians ranked dystocia among the most painful conditions of cattle (Huxley and Whay, 2006). This has even led to the assumption that parturient cows should be routinely treated with non-steroid anti-inflammatory drugs to relieve pain (Laven et al., 2012; Mainau et al., 2014; Newby et al., 2017; Gladden et al., 2018). The perception of labor-associated pain to some extent may be counteracted by an increase in the pain threshold. Such an increase in the pain threshold is mediated by the release of endogenous opioids or endorphins and has first been described in rats (Gintzler, 1980). Some degree of opioid-mediated analgesia at parturition exists in pigs (Jarvis et al., 1997) and an increased release of β -endorphin and met-enkephalin suggests similar mechanisms in parturient cows (Aurich et al., 1993). While on the one hand birth is characterized as

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stressful, on the other hand, it is assumed that parturient animals give birth only when they perceive the environment as safe and it is generally believed that external stressors inhibit the onset of parturition. In agreement with this assumption, under stud farm conditions over 90% of horse mares deliver their foal at night, when disturbance in the stable is at a minimum (Heidler et al., 2004). In contrast, in domestic ruminants, a predominance of night-time deliveries apparently does not exist. In cattle (Edwards, 1979) and sheep (Yamin et al., 1995) approximately 50% of deliveries take place during daylight hours and even a percentage of night-time calvings as low as 20% has been reported (Gleeson et al., 2007). The degree of maternal control over the onset of parturition may thus differ among domestic animal species.

The balance of activation and inhibition of the hypothalamo-pituitary-adrenocortical and the sympatho-adrenomedullary system in domestic animals at parturition so far is only partially understood. Activation of these systems is mainly interpreted as a physiological, stress-like response in association with parturition but could also be a reason for dystocia and decreased well-being in parturient animals. The role of external stressors on the onset and progress of parturition remains enigmatic and it is unclear to what extent stressful challenges either advance or delay the onset of parturition. This review summarizes current knowledge on stress-like responses in parturient animals and their role for the onset and fine-tuning of parturition. Emphasis is put on horses, ruminants and to some degree on pigs. Comparable studies in small companion animals so far remain rudimentary.

2. Hypothalamo-pituitary-adrenocortical activity in parturient animals

The cascade leading to the onset of parturition in domestic animals has first been described for sheep. Lambing is initiated by a sharp rise in cortisol secretion from the fetal adrenal glands. Acting on placental steroid biosynthesis, cortisol increases secretion of estrogens while progesterone synthesis decreases. The change in the ratio of estrogens to progesterone stimulates release of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), which in turn enhances the myometrial response to oxytocin and stimulates contractions (Liggins et al., 1977). Similarly, in horses and cattle, the initiation of parturition is preceded by an increase in fetal cortisol release (Comline et al., 1974; Fowden and Silver, 1995), whereas the signal of the porcine fetus for initiation of farrowing is not clear. Infusion of pig fetuses with ACTH does not induce delivery (Randall, 1990). Also, the role of the canine fetus, if any, for initiating whelping remains unclear.

Cortisol is not only the fetal signal that initiates parturition in many species but also essential for fetal maturation and preparation for the transition from intrauterine to extrauterine life (Liggins, 1994). In relation to gestation length of the respective species, the increase in fetal cortisol release in sheep and cattle occurs much earlier than in the equine fetus. Fetal cortisol release in horses increases only during the last two to three days before birth (Fowden and Silver, 1995). In agreement with this finding, viable calves are born after induction of parturition approximately two weeks before the expected day of calving (Zaremba et al., 1997) whereas in mares, induction of foaling at that time usually results in the birth of non-viable foals (Jeffcott and Rosedale, 1977; Fowden and Silver, 1995).

Cortisol release does not only increase in the late-gestation fetus but also in the antepartum dam. In horses, cortisol concentration in maternal plasma increases markedly in the last four days before parturition whereas salivary cortisol, representing the unbound and biologically active cortisol fraction, does not increase until two days before the foal is born (Nagel et al., 2012). The increase in maternal salivary cortisol before delivery coincides with the increase in fetal cortisol release (Fowden and Silver, 1995) and a decrease in maternal progesterone concentration (Ousey, 2004; Fowden et al., 2008; Nagel et al., 2012). The mechanisms that reduce progesterone synthesis in mares are, however, different from those in ewes (Challis et al., 2005). At the end of gestation, the fetoplacental unit controls equine progesterone metabolism, and pregnenolone from the fetal adrenal glands is the precursor of placental progesterone production (Haluska and Currie, 1988). With maturation of the fetus shortly before birth, fetal adrenal steroid synthesis switches from pregnenolone to cortisol, thus reducing and finally terminating the placental synthesis of pregnancy-maintaining progestins (Fowden et al., 2008). In cattle, fetal cortisol concentration increases during the last week of gestation (Comline et al., 1974) and stimulates uterine $PGF_{2\alpha}$ synthesis, which in turn initiates luteolysis and activates placental estrogen synthesis (Comline et al., 1974; Königsson et al., 2001). Maternal plasma cortisol concentration increases during the last one to two days before calving (Smith et al., 1973; Taverne et al., 1988; Patel et al., 1996) while salivary cortisol concentration only increases during the last hours before rupture of the fetal membranes (Nagel et al., 2016a). In horses as in ruminants, only little placental transfer of cortisol occurs in either direction (Comline et al., 1974; Nathanielsz et al., 1975). Because part of ^{14}C -labeled cortisol infused into the equine fetus diffused into the maternal circulation, it has been assumed that placental transfer of endogenous cortisol from the fetus to the mother is, however, possible during the last weeks of gestation (Nathanielsz et al., 1975).

The antepartum fetal and maternal cortisol increase in the domestic animal species studied so far is part of the endocrine changes that initiate parturition and does not represent a stress-like response (Challis et al., 2005). Cortisol increases further in parturient mares and cows. We suggest that this transient and pronounced increase in cortisol release directly at parturition is related to some degree of stress and by inference pain perceived by the dam during labor and expulsion of the neonate (Hydbring et al., 1999; Nagel et al., 2012).

In mares at foaling, cortisol concentration is markedly increased compared to the already elevated prepartum values (Nagel et al., 2012) but this is restricted to the short expulsive phase of foaling which often lasts less than 15 min (Melchert et al., 2019). The acute and transient increase in cortisol concentration most likely represents a stress-induced adrenocortical activation at foaling. Cortisol concentration in maternal blood during expulsion of the foal is more than threefold higher than in horses exposed to known stressful challenges such as road transport (Baucus et al., 1990), acute abdominal disease, traumatic conditions (Ayala et al., 2012) or abdominal surgery (Stegmann and Jones, 1998). Exposure of parturient mares to an experimental stressor during the expulsive phase of foaling (transfer to a new stable) did not further increase cortisol release. Expulsion of the foal may be perceived as a marked stressor already in undisturbed foaling and cortisol concentration was thus not further increased by an additional experimental challenge

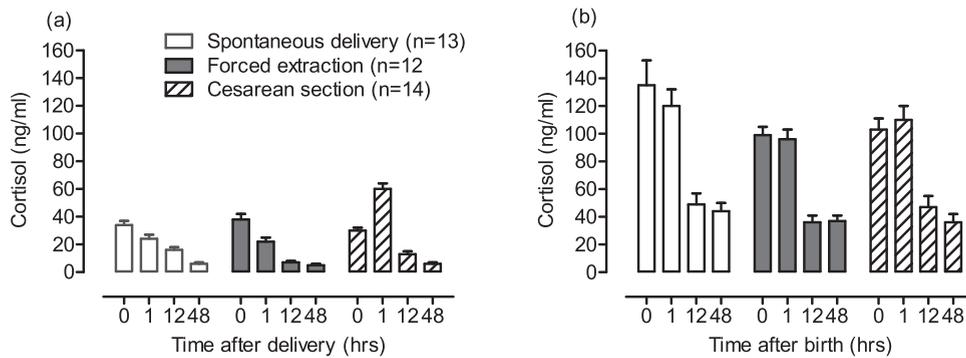


Fig. 1. Cortisol concentration in plasma of (a) cows with spontaneous calving, forced extraction and Cesarean section and (b) their newborn calves (Dobriniski and Aurich, unpublished).

(Melchert et al., 2019). Because the study did not include mares with dystocia, an even more pronounced cortisol release in such mares cannot be excluded.

Also in cattle, cortisol release increases further above an already elevated prepartum baseline during labor and expulsion of the calf (Hydbring et al., 1999; Vannucchi et al., 2015; Nagel et al., 2016b). Cortisol concentration peaked at or shortly after delivery of the calf (Hydbring et al., 1999; Nagel et al., 2016b) or, in goats, birth of the first kid (Hydbring et al., 1997, 1999). Conflicting reports exist on the effects of dystocia on cortisol release in parturient cows. We could not demonstrate differences between cows calving unassisted and those with assisted vaginal deliveries (Dobriniski and Aurich, unpublished; Fig. 1a), whereas others have reported higher cortisol concentrations in cows with dystocia (Vannucchi et al., 2015) or giving birth to twins (Patel et al., 1996) in comparison to unassisted singleton calvings. Furthermore, salivary cortisol concentration was higher in cows calving spontaneously at term than in cows with induced parturition. This indicates that calving is less stressful for the dam when smaller calves are born as occurs with induced preterm calving (Nagel et al., 2016a, b). In cows requiring Cesarean section, cortisol concentration in plasma was nearly twofold higher during surgery compared to values during maximal labor but before the Cesarean section (Dobriniski and Aurich, unpublished; Fig. 1a). The animals' stress response to the surgical intervention thus exceeds the stress of calving and dystocia.

As in ruminants and horses, hypothalamo-anterior pituitary adrenocortical (HPA) activity is elevated in parturient sows. Cortisol concentration in plasma further increases with piglet number during farrowing. This increase is accompanied by constantly rising concentrations of plasma β -endorphin. Parturition itself thus stimulates adrenocortical activity, most likely as a result of pain and/or stress induced by uterine contractions and movement of piglets through the birth canal (Jarvis et al., 1997, 1998, 1999).

In the peripartum period, maternal plasma cortisol concentration increases also in dogs (Concannon et al., 1978; Veronesi et al., 2002). A further acute and more pronounced elevation in cortisol release occurs at birth. Cortisol concentration peaked at delivery of the first puppy, remained high during birth of the second puppy and then declined while plasma oxytocin concentration remained elevated throughout labor, indicating stress during initiation of labour (Olsson et al., 2003).

3. Sympatho-adrenomedullary activity in parturient animals

Sympatho-adrenomedullary activity in periparturient domestic animals can be assessed directly by analysis of catecholamine release or indirectly via determination of heart rate and heart rate variability (HRV; e.g. Hydbring et al., 1997; Nagel et al., 2012, 2014, 2016b; Melchert et al., 2019). Heart rate is never constant and characterised by short-term variability of the beat-to-beat interval. This variability represents fine-tuning of the cardiac beat-to-beat control mechanisms by the autonomous nervous system. An increase in HRV indicates parasympathetic dominance while decreasing HRV reflects increasing sympathetic tone such as during stressful situations or physical activity (von Borell et al., 2007). Fetal HRV reflects also maturation of the autonomous nervous system, resulting in increasing parasympathetic activity with ongoing gestation (van Leeuwen et al., 1999).

Fetomaternal electrocardiography allows continuous heart rate recordings not only in the mother but in monotocous species also in her fetus. In horses, this technique has been first documented nearly 100 years ago (Nörr, 1921), but has become routine in veterinary medicine only in the last decade when portable electrocardiogram (ECG) recorders became available. Modern ECG devices separate fetal and maternal recordings with a software filter and amplify the fetal signal. Fetomaternal electrocardiography thus allows non-invasive and continuous recording of fetal and maternal heart rate during late pregnancy and the initial stages of parturition in cattle (Trenk et al., 2015; Nagel et al., 2016a, b) and throughout parturition in horses (Nagel et al., 2010, 2012, 2014, 2015). In horses, fetal cardiac signals could be determined from mid-gestation onwards (Parkes and Colles, 1977; Buss et al., 1980; Nagel et al., 2010) but occasional detection of a fetal signal already around day 120 of gestation has been reported (Baska-Vincze et al., 2015). In cattle, the cardiac signal of a living fetus can reliably be detected from day 185 of gestation onwards (Trenk et al., 2015). Differences in reliability of detection of fetal cardiac activity are due to gestational age and size of the dam and her fetus.

Gestational age is negatively correlated with fetal heart rate and positively correlated with fetal HRV in both horses and cattle (Nagel et al., 2010, 2012; Trenk et al., 2015; Nagel et al., 2016a). At 80% of gestation length (around 270 days in horses and 230 in cattle), fetal heart rate approximates 100 beats/min in the equine (Nagel et al., 2010) and 130 beats/min in the bovine fetus (Trenk

et al., 2015). Until the last days before birth, fetal heart rate decreases to 80 beats/min in horses (Nagel et al., 2010, 2012) and 105 beats/min in cattle (Trenk et al., 2015; Nagel et al., 2016a). Thus, during the last 20% of gestation, fetal heart rate decreases to the same extent in both species. A higher fetal heart rate in cattle than in horses is in agreement with a higher resting heart rate in adult cattle compared to horses. Within a species, size of the dam and her fetus has no major influence on late gestation fetal heart rate although maternal heart rate is inversely correlated to size of the dam. Fetal heart rate neither differed between small (Shetland pony) and large (Warmblood) equine fetuses (Nagel et al., 2011b) nor between bovine fetuses carried by first-calf heifers and pluriparous cows (Trenk et al., 2015).

While fetal heart rate decreases, fetal HRV in horses increases during the last 20% of gestation but remains largely constant in the last week before birth (Nagel et al., 2010, 2012). In contrast, in the bovine fetus, HRV increases constantly until birth (Trenk et al., 2015; Nagel et al., 2016a). The final increase in fetal HRV in cattle before birth coincides with rising concentrations of cortisol in fetal blood (Comline et al., 1974; Taverne et al., 1988; Fowden and Silver, 1995). The different time of increasing fetal HRV in fetal foals and calves reflects differences in their final maturation (Nagel et al., 2016a).

The increase in HRV of fetuses from pluriparous cows in the last week before birth is lacking in fetuses carried by first-calf heifers (Trenk et al., 2015). Reduced HRV in fetuses carried by heifers may indicate a stress-like response. A smaller cotyledonary surface in heifers and restricted nutrient availability for the fetus compared to pluriparous cows has been demonstrated (van Eetvelde et al., 2016). Thus, in heifers, a limit in placental nutrient and oxygen supply to the fetus may exist close to term and induce a fetal stress response. This interpretation is also in agreement with a slightly shorter gestation length in heifers versus cows, i.e. an earlier onset of the fetal cortisol signal leading to parturition.

In pregnant mares and cows, the increasing nutrient and oxygen demands of the fetus are met by an increased uterine blood flow. This has in part been attributed to an increase in uterine blood vessel diameter (Bollwein et al., 2004; Herzog et al., 2011; Klewitz et al., 2015) but an increase in heart rate accounts for most of the increase in cardiac output during pregnancy. The late gestation increase in maternal heart rate reflects successful adaptation of the cardiovascular system of the pregnant dam to the rising demands of the growing fetus (Brosh et al., 2002; Nagel et al., 2011a, 2012; Trenk et al., 2015; Nagel et al., 2016a, c). Whereas maternal heart rate increases with the demands of lactation and fetal growth, maternal HRV does not change during late gestation in horse mares (Nagel et al., 2011a) and in cattle (Mohr et al., 2002; Trenk et al., 2015; Nagel et al., 2016b). Although the maternal burden increases towards term, based on HRV there is no evidence that maternal sympathoadrenal activity increases due to gestation in cattle and horses.

During physiological labor and expulsion of the foal, heart rate does not change in parturient mares despite existence of a marked cortisol release (Nagel et al., 2014). In cattle, heart rate starts to increase during the first stage of labor (Kovács et al., 2015; Nagel et al., 2016b) and well before salivary cortisol concentration increases (Nagel et al., 2016b). In contrast to cortisol which peaks at or shortly after the end of parturition (Nagel et al., 2014, 2016b), maternal heart rate in mares decreases immediately after birth of the foal (Nagel et al., 2014). In the cow, heart rate is elevated during the first hour after parturition (Kovács et al., 2015; Nagel et al., 2016b) and thus longer than in mares (Fig. 2).

In parturient cows, HRV increases gradually and peaks shortly before the calf is born, indicating a stepwise shift in sympathovagal balance towards parasympathetic dominance. (Kovács et al., 2015; Nagel et al., 2016b). Parasympathetic tone is lower in spontaneously calving cows than in cows with induced preterm labor (Nagel et al., 2016b) and negatively correlated to increasing birth weight of the calf (Kovács et al., 2015). This indicates a more pronounced stress at birth of heavier calves. In horse mares, HRV maxima occur not during but shortly after foaling. In both species, HRV decreases rapidly thereafter (Nagel et al., 2012, 2014; Kovács et al., 2015; Nagel et al., 2016b). Expulsion of the neonate is thus dominated by parasympathetic activity. Interestingly, the increase in plasma oxytocin concentration at foaling is restricted to the short phase of parasympathetic dominance (Haluska and Currie, 1988; Vivrette et al., 2000; Melchert et al., 2019) that coincides with expulsion of the foal. A cause-effect relationship, however, can largely be excluded because oxytocin treatment did not change cardiovascular parameters in parturient mares (Nagel et al., 2017).

The most striking evidence of parasympathetic dominance during labor is the occurrence of sinus arrhythmias. These exist in 80% of foaling mares (Nagel et al., 2014) and 60% of calving cows (Nagel et al., 2016b). Cardiac arrhythmias were identified as second-degree atrioventricular blocks in horses (Nagel et al., 2014, 2016c). Due to the position of the fetomaternal ECG electrodes in cattle, it

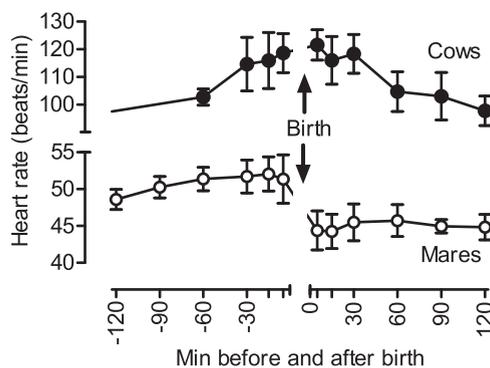


Fig. 2. Heart rate in parturient mares and cows from 2 h before to 2 h after delivery (adapted from Nagel et al., 2014, 2016b).

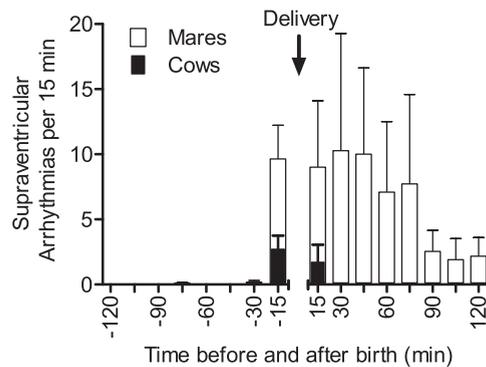


Fig. 3. Number of supraventricular arrhythmias per 15 min intervals in mares and cows from 2 h before to 2 h after delivery (adapted from Nagel et al., 2014, 2016b).

remains unclear if the cardiac arrhythmias at calving represent sinoatrial arrhythmias or atrioventricular blocks (Nagel et al., 2016b). In horse mares but not in cows, atrioventricular blocks persist for several hours after parturition (Nagel et al., 2014; 2016c; Fig. 3).

In conclusion, the initial phases of parturition appear to be stressful especially in cows but the expulsive phase of labor in mares and cows with physiological parturition is characterized by a strong parasympathetic tone. This is further supported by largely unchanged concentrations of catecholamines in plasma of mares (Nagel et al., 2014) and cows (Hydbring et al., 1999) during the expulsive phase of labor. We thus suggest that in cattle and horses, expulsion of the fetus is promoted by parasympathetic dominance.

4. Prepartum stress and the onset of parturition

Fetal maturation triggers increasing cortisol synthesis that initiates the onset of parturition. It could thus be hypothesized that situations associated with either a pronounced or prolonged elevation in maternal cortisol release may advance the onset of parturition in late-pregnant animals. Road transport is a stressor for horses and cattle and elicits a complex stress response including cortisol release (Baucus et al., 1990; Zdunczyk et al., 1991; Schmidt et al., 2010a,b,c). Although late pregnant animals occasionally need to be transported, there is surprisingly little information on possible interactions between transport-stress and parturition.

In late pregnant cows transported by road for 1.5 h, cortisol concentrations increased markedly and one out of 10 cows subsequently aborted. This suggests that already a short-distance transport was perceived as a stressor but relations between transport stress and abortion or preterm birth in cows remain unclear (Zdunczyk et al., 1991). In a recent study from our group, pregnant horse mares were either transported for 3 h by road or remained in the foaling stable as controls. The experiment was started when mares were well prepared but not yet ready for foaling. Relative time of foaling was calculated as time from precolostrum pH decrease to 6.5 to onset of parturition. Transport not only elicited increased cortisol concentration but also significantly advanced the time of foaling (42 ± 9 h in transported and 116 ± 28 h in control mares; Nagel et al., 2018). The placenta was released within one hour after delivery in transported as well as in control mares (Nagel, unpublished).

5. Intrapartum stress and the progress of parturition

External stressors may interrupt parturition and delay birth via two different mechanisms. Stressful situations shift the autonomous nervous system towards sympathetic dominance that may inhibit labor via activation of myometrial β_2 -receptors. Additionally, external stressors at parturition may induce an increase in central nervous system opioidergic tone, which in turn may inhibit oxytocin release.

Studies on stress and the progress of parturition so far have largely focussed on polytocous species such as the rat, mouse and pig. Transferring parturient dams after birth of the first pup or piglet, respectively, to an unfamiliar and therefore stressful environment reduced oxytocin release and prolonged the time interval until delivery of the next littermate (Newton et al., 1968; Leng et al., 1985, 1988; Lawrence et al., 1992; Douglas et al., 2002). In rats (Leng et al., 1987, 1988) and pigs (Lawrence et al., 1992, 1997) but not in mice (Douglas et al., 2002) these effects were reversed by administration of the opioid antagonist naloxone, indicating that in rats and pigs stressors slow parturition via an opioidergic tone which in turn restrains oxytocin release. In contrast, in mice, β -adrenergic antagonists counteracted the stress-induced delay of subsequent deliveries, whereas β -agonists delayed birth in non-stressed mice. This indicates that in mice sympathoadrenal activity contributes to stress-delayed births (Douglas et al., 2002).

A recent study of our group used a similar experimental design in horses and thus for the first time in a monotocous species (Melchert et al., 2019). Foaling mares were transferred from their familiar, straw-bedded and dimmed foaling stable to an unfamiliar, brightly lightened stable with only rubber mats on the floor as soon as fetal membrane rupture was detected. This potentially stressful challenge increased the time until complete birth of the foal from approximately 5 min in control mares to 10 min. This transfer of mares to a novel environment delayed primarily the onset of foal expulsion, i.e. the time until passage of the fetal feet through the vulva of the mare. Progression of the foal through the birth canal then resumed and there was no prolonged inhibition of labor. Whereas HRV increased in control mares, this increase was reduced and delayed in stressed mares, but accompanied by a more

pronounced release of epinephrine and norepinephrine. The treatment was, however, without effect on oxytocin release. This may indicate that the stress-induced prolongation of foaling in mares is mediated via increased sympathetic activity and not via an inhibition of oxytocin release (Melchert et al., 2019). The mechanisms in the monotocous horse therefore appear to resemble those in mice (Newton et al., 1968; Douglas et al., 2002) and not in rats (Leng et al., 1985, 1988) and pigs (Lawrence et al., 1992, 1997).

Time from birth of the foal until release of the fetal membranes tended to be longer in stressed than in non-stressed mares (Melchert et al., 2019). A stress-induced delay of the expulsive phase (stage 2) at birth thus may extend into stage 3 of foaling. Inadequate expression of oxytocin receptors has recently been suggested as a cause of uterine atony and fetal membrane retention (Rapacz-Leonard et al., 2015), however, effects of acute stress on myometrial oxytocin receptors have not been studied so far.

In agreement with findings in horses, increased sympathetic activity as evidenced from reduced HRV was demonstrated in parturient cows disturbed during an early stage of calving by inappropriate farmer intervention. This induced a more pronounced increase in maternal heart rate and prevented the increase in HRV that occurs physiologically in unassisted calvings (Kovács et al., 2015, 2016). Because farmer intervention resulted in rapid, assisted delivery of the calf, the progress of parturition could not be determined in these cows. An inhibition of labor with β_2 -receptor agonists in cattle has, however, been demonstrated in an older study (Putnam et al., 1985).

Whereas the acute stress of moving animals to a new and uncomfortable environment prolonged parturition, transferring gilts before the expected farrowing date from a straw-bedded pen into a farrowing crate without straw did neither enhance the farrowing-induced increase in cortisol concentration nor did it prolong the process of farrowing itself (Jarvis et al., 1998, 1999). Although previous work on cortisol during the pre-farrowing period has shown that crates without straw are perceived as more stressful than straw-bedded pens (Jarvis et al., 1997), parturient sows apparently adapt to this less comfortable housing system to a degree that does prevent disturbances of parturition by the environment (Lawrence et al., 1994; Jarvis et al., 1998, 1999). Parturition was also not interrupted following space restriction of gilts and maternal space during farrowing is apparently no major stressor (Gilbert et al., 1997).

In conclusion, in mares and cows, an increased sympathetic tone can transiently override the strong parasympathetic dominance of physiological parturition. In sows, acute stress delays birth of piglets via an opioid-mediated reduction in oxytocin release. Prolonged and chronic stressors such as an uncomfortable housing system to which sows are given time to adapt are without effect on the progress of farrowing.

6. Neonatal stress response and neonatal adaptation

Birth and the demands of immediate adaptation to the extrauterine environment are amongst the most stressful events of life. Cortisol concentrations in newborn calves and foals are much higher after birth than in the fetus before onset of labor (Comline et al., 1974; Fowden and Silver, 1995). Cortisol concentration in calves was higher immediately after spontaneous birth than directly after forced extraction or Cesarean section (Dobrinski and Aurich, unpublished; Fig 1b), suggesting that already uncomplicated birth induces maximal stimulation of HPA activity. However, adrenomedullary depletion may have occurred after prolonged calving requiring veterinary assistance.

In horses, once foaling is initiated and the fetal membranes have ruptured, parturition proceeds rapidly and the foal is usually born within less than 15 min (Neuhauser et al., 2008; Nagel et al., 2010, 2012, 2014). In cattle, the time interval from fetal membrane rupture to complete birth of the calf lasts between one and two hours (Grunert, 1993). Uterine contractions during labor decrease uterine blood supply and result in a variable degree of fetal hypoxia. This leads to a parasympathetic-mediated decrease in fetal heart rate and episodic heart rate decelerations during labor (Jonker et al., 1991). Persistent hypoxia stimulates sympathoadrenal activity with a pronounced catecholamine release in calves (Aurich et al., 1993) and lambs (Eliot et al., 1981; Padbury et al., 1988) exposed to uterine contractions. Furthermore, birth is associated with a marked cortisol release in calves (Aurich et al., 1990; Hoyer et al., 1990; Aurich et al., 1993; Nagel et al., 2016a) and in foals (Fowden and Silver, 1995; Nagel et al., 2012, 2015). In calves, also concentrations of epinephrine and norepinephrine in plasma are high at birth (Aurich et al., 1990). While cortisol concentration increases further after birth (Nagel et al., 2016a), catecholamine concentrations decrease rapidly (Aurich et al., 1990). By stimulating energy mobilisation, thermogenesis, pulmonary surfactant release, respiration and cardiac function, catecholamines and cortisol promote adaptation of the neonate to the extrauterine environment after birth (Irestedt et al., 1982; Downing and Lee, 1983; Padbury et al., 1987; Aurich et al., 1990; Hoyer et al., 1990). The initial stimulatory phase is followed by an increased release of enkephalins after umbilical cord rupture. Enkephalins are co-stored with catecholamines in the adrenal medulla and inhibit catecholamine release (Aurich et al., 1993).

Although a stress response is induced at birth in calves and in foals, cattle and horses differ with regard to the timing of this response. In calves, the release of cortisol and catecholamines as well as heart rate increase markedly already during labor (Aurich et al., 1990; Hoyer et al., 1990; Nagel et al., 2016a). In contrast, in foals, physiological birth itself is not associated with an increase in heart rate. Instead, heart rate even decreases from approximately 80 beats/min 120 min before birth to 60 beats/min at 5 min before birth. During delivery, fetal HRV in foals and calves remains largely stable (Nagel et al., 2015, 2016a) but an increase in fetal heart rate decelerations and a lack of transient heart rate increases have been demonstrated in cattle (Jonker et al., 1989, 1991). In both equine and bovine neonates, the immediate postnatal period is associated with a marked rise in heart rate (Fig. 4) and a decrease in HRV, indicative of high sympathetic activity, and an increase in cortisol concentration. This suggests a pronounced stress-like response once the foal or calf is born (Nagel et al., 2015; 2016a; Dobrinski and Aurich, unpublished; Fig. 1b). Cortisol concentration peaks at 60 min after birth in the equine and 30 to 60 min in the bovine neonate and is already markedly lower 4 h later (Nagel et al., 2016a; Wulf et al., 2017).

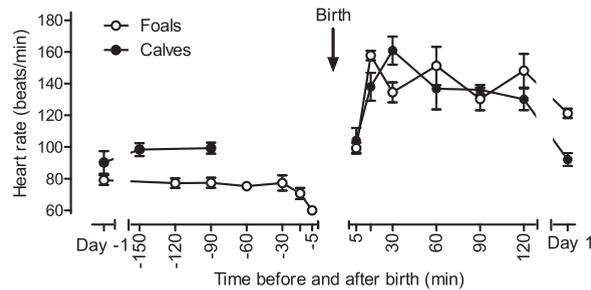


Fig. 4. Changes at birth in fetal and neonatal heart rate of foals and calves (adapted from Nagel et al., 2015, 2016a). Nagel et al., Fig. 4.

7. Conclusions

Stress effects on the initiation and the progress of parturition in domestic animals so far are only partially investigated. Increased cortisol release in preparturient animals is part of the endocrine changes that initiate parturition. Cortisol release increases further directly at parturition and this transient and pronounced increase is related to stress and by inference pain perceived by the parturient dam. While the initial phase of parturition appears to be stressful especially in cows, the expulsive phase of labor in mares and cows is characterised by strong parasympathetic dominance, which probably is a prerequisite for rapid expulsion of the fetus. Late pregnant cows and mares perceive a short-distance road transport as stress. Transport by road advanced the time of foaling in mares but relations between transport stress and preterm birth in cows are currently unclear. During parturition itself, increased sympathetic activity can transiently override the strong parasympathetic dominance of physiological parturition in mares and cows while in pigs external stressors may delay delivery of piglets via reduced oxytocin release. Because of potential negative effects on the dam and fetus, acute disturbance and manipulation of parturient animals thus should be avoided unless there is a clear indication for veterinary intervention. For the newborn, birth and immediate adaptation to the extrauterine environment are amongst the most stressful events of life. A marked release of cortisol and high sympathetic activity at birth enhance rapid adaptation of the newborn to extrauterine life.

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