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Effect of altrenogest-treatment of mares in late gestation on adrenocortical function, blood count and plasma electrolytes in their foals

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Keywords: horse; pregnancy; foal; altrenogest; cortisol

Summary

Reasons for performing study: **Mares with compromised pregnancies are often treated with altrenogest to prevent abortion. However, there is only limited information about effects on the foal when altrenogest treatment is continued during final maturation of the fetus.**

Objectives: **To determine effects of altrenogest treatment during late gestation in mares on maturity, haematology changes, adrenocortical function and serum electrolytes in their newborn foals.**

Methods: **Six mares were treated with altrenogest (0.088 mg/kg bwt) once daily from Day 280 of pregnancy until foaling and 7 mares served as controls.**

Results: **Foals born to altrenogest-treated mares had a significantly lower neutrophil/lymphocyte ratio on the first day after birth than control foals (P<0.05). Basal plasma cortisol concentrations immediately after birth were higher in foals of altrenogest-treated mares than in control foals (P<0.05). Cortisol release in response to exogenous adrenocorticotropic hormone (ACTH) - except for higher values 15 min after ACTH injection in foals of altrenogest-treated mares on Day 1 - revealed no differences in adrenocortical function between the groups of foals. Plasma potassium concentration in foals from altrenogest-treated mares compared to control foals was significantly lower immediately after birth (P<0.05) and plasma ionised calcium concentration was significantly lower 3 h after birth (P = 0.01).**

Conclusions and potential relevance: **Altrenogest treatment of pregnant mares prolonged labour had no major effects on adrenocortical function in foals. A reduced neutrophil/ lymphocyte ratio in these foals may suggest either immunomodulatory effects of altrenogest or dysmaturity of the foals.**

Introduction

Mares with compromised pregnancies are often treated with the synthetic gestagen altrenogest in order to maintain pregnancy and prevent abortion or delivery of an immature foal (Macpherson 2005). It is believed that this maintains myometrial quiescence and therefore prolongs pregnancy until term. In clinical cases, it is difficult to decide at what time altrenogest should be given in respect to the expected date of foaling. If the treatment is stopped too early this might result in premature birth of a nonviable foal. In contrast, if treatment is continued too long, this might block the onset of labour and prevent delivery of the foal.

However, only limited information exists on the effects of altrenogest on parturition itself, final maturation of the fetus and neonatal adaptation to the extrauterine environment. If treatment is terminated several days before the physiological end of gestation, no detrimental effects on parturition and on viability of foals born some days after cessation of treatments were found (Shoemaker *et al*. 1989; Ousey *et al*. 2002). In a recent study (Neuhauser *et al*. 2008) continuous altrenogest treatment, starting on Day 280 of gestation, did not prevent parturition, which occurred slightly earlier than in control mares, prolonged labour and foals more often had adaptive problems after birth than control foals.

Here haematological changes, adrenocortical function and serum electrolytes in foals born after altrenogest treatment to their dams and in control foals are reported. Haematological changes are indicative for maturity of the foal and the neutrophil/ lymphocyte (N/L) ratio is a useful index for assessing the foal's readiness for birth (Jeffcott *et al*. 1982). Corticosteroids play a major role in maturation of the fetus before birth (Liggins 1976). In the equine fetus, adrenal maturation occurs and plasma cortisol levels increase only a few days before birth (Silver and Fowden 1994). A pronounced cortisol release in response to adrenocorticotropic hormone (ACTH) exists only in term foals (Rossdale *et al*. 1982; Silver *et al*. 1984). Therefore, after birth, normal full-term foals have high plasma cortisol concentrations while the adrenal gland of premature foals is not able to secrete cortisol (Rossdale *et al*. 1973, 1982; Nathanielsz *et al*. 1975; Silver *et al*. 1984, 1991). In septic and convulsive foals, plasma cortisol levels are higher than in healthy foals (Rossdale *et al*. 1973, 1995; Gold *et al*. 2007).

Mineralocorticoids are important for fluid and electrolyte balance (Greco and Stabenfeldt 1997). The renin angiotensin aldosterone system is more activated during pregnancy, fetal and neonatal life (Katz *et al*. 1974; Shaftoe 1990). After premature

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delivery, there is an exaggerated response of this system and foals fail to maintain serum electrolyte concentration (Pipkin *et al*. 1984). Alterations of serum electrolyte concentrations can be associated with a variety of disorders in the neonatal foal (Bauer 1990).

The aim of this study was to determine maturity and health in foals born to altrenogest-treated mares by assessing N/L ratio, adrenocortical function and serum electrolytes. Clinical data in the same foals, indicating prolonged parturition and disturbed perinatal adaptation have been reported recently (Neuhauser *et al*. 2008).

Materials and methods

Animals

Eight Shetland mares aged 4–14 years were inseminated in 2 consecutive years with semen from pony stallions. The oestrous cycle of the mares was checked regularly by transrectal ultrasound of the uterus and ovaries, vaginal inspection with a speculum and by investigation of oestrous behaviour with a stallion. Mares were inseminated every other day during oestrus and the first day a *corpus luteum* could be determined (transrectal ultrasound) was designated as Day 1 of gestation. Animals were kept in outdoor paddocks or in a straw bedded indoor group stable depending on the weather until Day 300 of gestation. Thereafter, mares were transferred to straw bedded individual boxes and monitored continuously until parturition. Ponies were fed hay twice daily and had free access to water and mineral supplements.

Experimental design

Mares were divided randomly into 2 treatment orders with half of the mares receiving 0.088 mg/kg bwt altrenogest (Regumate)[1] orally once daily starting on Day 280 of gestation until foaling in the first year and no treatment in the second year. The other half of the mares was treated in opposite order. Three mares lost their pregnancy between Days 40 and 270 and were excluded from the experiment bringing the number of animals to 6 in the treatment group and 7 in the control group. The experiment was performed according to Austrian animal welfare legislation and was approved by the Austrian Ministry of Science (license number BMBWK-68.205/0020-BrGT/2006).

Gestational length, duration of parturition, and clinical and acid-base parameters in the foals were monitored closely and have been reported previously (Neuhauser *et al*. 2008). In brief, out of 6 foals in the altrenogest group one died due to dystocia (displacement of the head), one foal died 30 min after birth due to respiratory depression, and another from the altrenogest group had to be resuscitated by oxygen insufflation into the nostril at 30 min after birth but did not receive any stimulatory drugs. The number of foals in the treatment group was thus 5 until 30 min after birth and 4 thereafter. Gestational length tended to be shorter in mares given altrenogest (mean ± s.d. 320 ± 4 vs. 328 ± 2 days in controls, not significant). Birth weight of the foals did not differ between groups. The second stage of parturition was 12.1 ± 2.4 min in altrenogest-treated mares and 5.8 ± 1.1 min in control mares (P = 0.07). Time from birth to first standing (altrenogest 27.0 ± 4.4, control 30.1 ± 4.5 min) and to first suck (altrenogest 114.2 ± 33.3, control 102.1 ± 12.5 min) did not differ between groups.

Experimental procedures

Blood samples from the foals were taken via a jugular vein catheter (Milacath)[2] plus extension set placed directly after birth. Samples for cortisol determination were withdrawn immediately and at 15, 30, 45 and 60 min after birth, and every hour thereafter until 12 h and then at 24, 36 and 48 h after birth. Samples for haematology were taken on Days 1, 2 and 5 after birth. Blood for cortisol determination and haematology was collected into EDTA-containing tubes (Vacuette)[3], for cortisol measurement was centrifuged immediately at 950 ***g*** for 10 min (Mikro 22 R)[4] and plasma was stored at -20ºC until analysis. For determination of haematology, an automatic blood cell counter (ADVIA 120)[5] with adapted veterinary software was used. Blood cell differentials were checked by microscopy on Wright stained blood smears, when scattergrams indicated problems with automated differentiation.

For analysis of electrolytes, blood was collected into heparinised syringes (PICO50)[6] and electrolyte values were determined by an automatic blood gas analyser (ABL77)[6].

An ACTH stimulation test was performed on Days 1 (16–18 h after birth) and on Day 5 to determine adrenocortical response. ACTH (0.125 mg; Synacthen)[7] was given i.m. at time 0 in the foals of both groups. Blood samples were collected via a jugular vein catheter 30 min and immediately before (basal values) and at 5, 15, 30, 60, 90 and 120 min after ACTH-injection.

Plasma concentrations of cortisol were measured after extraction with diethylether with a competitive biotin-labelled enzyme immunoassay as described (Palme and Möstl 1997). The intra- and interassay coefficients of variation were 8.9 and 19.9%, respectively, and the minimal detectable concentration was 0.3 pg/well.

Statistical analysis

All statistical analyses were made with the SPSS statistics package[8]. Because data were not normally distributed, nonparametric tests were used. Comparisons between treatments were made by Mann-Whitney test. Cortisol release in response to

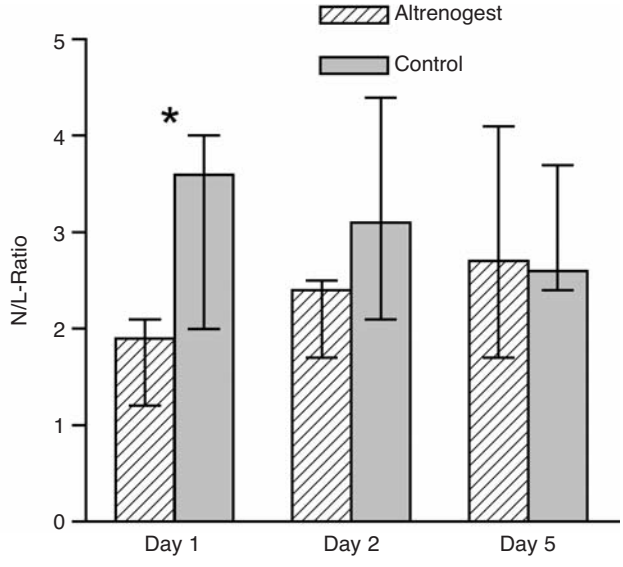

*Fig 1: Neutrophil/lymphocyte (N/L) ratio in foals born to mares treated with altrenogest and in control foals on Days 1, 2 and 5 after birth, *P<0.05 (data are median and interquartile range; altrenogest: n = 5 on Day 1, n = 4 on Days 2 and 5, control: n = 7).*

TABLE 1: Haematological parameters of foals born to altrenogest-treated mares and control foals during the first days *post partum* (data given are median and interquartile range)

	Day 1 *post partum*		Day 2 *post partum*		Day 5 *post partum*	
	Altrenogest (n = 5)	Control (n = 7)	Altrenogest (n = 4)	Control (n = 7)	Altrenogest (n = 4)	Control (n = 7)
Erythrocytes (x 10^{12}/l)	9.2 (7.8–9.8)	9.9 (8.8–10.1)	8.6 (7.9–9.7)	8.9 (8.6–9.2)	8.2 (6.7–9.1)	8.7 (7.3–9.0)
Haemoglobin (g/l)	132 (119–142)	138 (129–148)	124 (111–136)	129 (124–139)	112 (97–129)	117 (109–130)
PCV (%)	33.4 (30.8–35.7)	34.3 (33.3–37.0)	31.2 (38.7–34.6)	31.5 (30.5–34.3)	28.8 (24.6–33.6)	30.5 (27.2–32.6)
MCV (fl)	36.9 (35.7–40.2)	37.3 (33.8–39.2)	35.5 (34.4–38.9)	35.9 (34.7–38.6)	34.4 (33.0–37.3)	35.1 (33.5–37.3)
MCHC (g/l)	394 (386–399)	402 (393–405)	388 (385–403)	407 (405–410)	397 (392–414)	409 (401–413)
MCH (pg)	14.5 (14.0–15.8)	14.9 (13.6–15.7)	14.2 (13.8–15.2)	14.6 (14.2–15.7)	14.1 (13.1–14.9)	14.3 (13-4–15.4)
Leucocytes (x 10^6/l)	6550 (5665–8710)	7080 (6120–9750)	6070 (5038–7193)	6240 (4990–8240)	9035 (6205–9900)	6370 (5140–7400)
Lymphocytes (x 10^6/l)	2880 (1801–3195) (36%)	1950 (1628–2057) (22%)	1771 (1727–1987) (30%)	1542 (1187–2011) (24%)	2130 (1234–3199) (26%)	1226 (1067–1819) (22%)
Neutrophils (x 10^6/ll)	3931 (3427–4929) (58%)	5320 (3901–7410) (74%)	4175 (3061–4918) (66%)	4630 (3259–5859) (73%)	5282 (4067–6784) (65%)	4450 (2889–4869) (70%)
Eosinophils (x 10^6/l)	76 (29–228) (2%)	71 (18–106) (1%)	64 (36–96) (1%)	47 (34-70) (0.8%)	64 (40–116) (1%)	51 (22–95) (1%)
Basophils (x 10^6/l)	69 (46–342) (2%)	31 (18–131) (1%)	39 (31–50) (1%)	24 (1–51) (0.4%)	74 (66–83) (1%)	51 (45–74) (1%)
Monocytes (x 10^6/l)	66 (41–232) (2%)	123 (62–171) (2%)	71 (58–161) (2%)	80 (75–152) (1.8%)	499 (346–899) (7%)	418 (235–457) (6%)

PCV = packed cell volume; MCV = mean corpuscular volume; MCHC = mean corpuscular haemoglobin concentration; MCH mean corpuscular haemoglobin.

ACTH injection was also calculated as area under the curve for the time period from ACTH injection to 120 min thereafter and compared in the same animals between Days 1 and 5 by Wilcoxon test (paired samples). The relationship between plasma cortisol concentration and neutrophil/lymphocyte ratio on Days 1, 2 and 5 *post partum* was calculated by Pearson's correlation test. A P value <0.05 was considered significant. Data are given as median and interquartile range ($Q_{0.75}$–$Q_{0.25}$)

Results

Haematology

The neutrophil/lymphocyte (N/L) ratio was significantly lower in foals born to altrenogest-treated mares on the first day *post partum* (median 1.9, interquartile range 1.2–2.2 in foals of the treatment group and 3.6, range 2.0–4.0, in control foals, P<0.05). There was no significant difference in N/L ratio between the groups of foals on Days 2 and 5 (treatment group 2.4, range 1.7–2.5, and 2.7, range 1.7–4.1, respectively, control group 3.1, range 2.1–4.4 and 2.5, range 2.4–3.7, respectively, Fig 1). At no time were significant differences in the absolute numbers of white blood cells, erythrocytes, packed cell volume and erythrocyte indices (mean corpuscular volume, mean corpuscular haemoglobin concentration, mean corpuscular haemoglobin) between the foals of altrenogest-treated and untreated mares found (Table 1).

Basal cortisol concentration

Immediately after birth, plasma cortisol levels were significantly higher in foals of altrenogest-treated mares compared to untreated controls (34.4, range 17.1–40.0 ng/ml, vs. 15.6, range 10.7–18.7 ng/ml, P<0.05). After birth, plasma cortisol concentration increased in both groups and reached maximal levels at 30 min in foals of altrenogest treated mares (48.7, range 29.7–73.5 ng/ml) and at 45 min in controls (32.0, range 25.9–48.1 ng/ml). Thereafter cortisol levels declined. There were no differences in cortisol values between foals of treated and control mares from 15 min–48 h after birth (Fig 2).

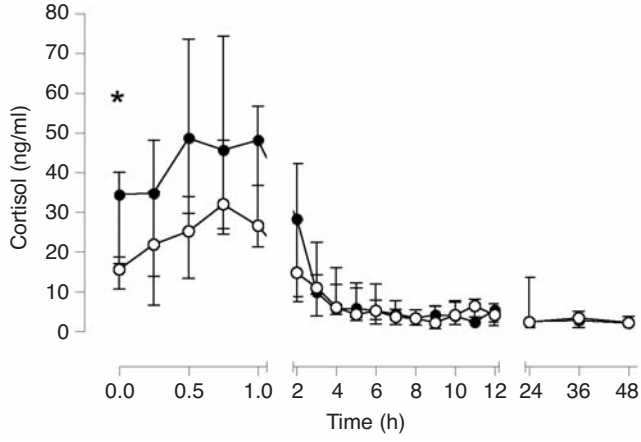

Fig 2: Plasma cortisol concentration during the first 48 h post partum *in foals born to mares treated with altrenogest (●) and in control foals (○), * P<0.05 (data are median and interquartile range; altrenogest: n = 5 until 30 min and n = 4 thereafter, control: n = 7).*

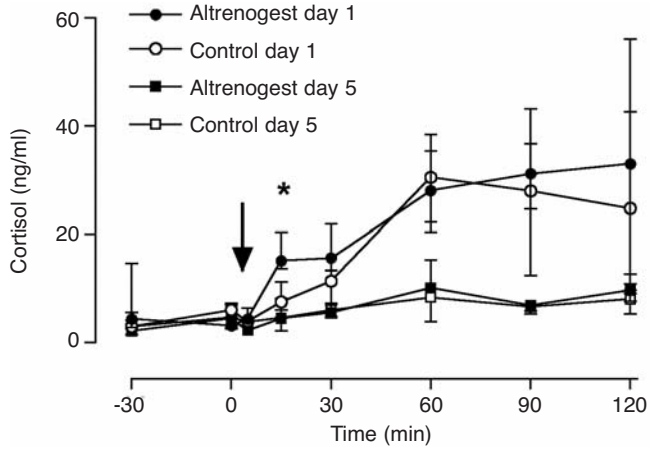

*Fig 3: Plasma cortisol concentration after injection of ACTH (arrow) on Days 1 and 5 after birth in foals born to mares treated with altrenogest (●) and in control foals (○), * P<0.05 (data are median and interquartile range; altrenogest: n = 4, control: n = 7).*

No significant correlation between N/L ratio and plasma cortisol values on Days 1 and 5 of life could be demonstrated (r = 0.180 and r = 0.458) but at 48 h after birth there was a significant correlation between these parameters (r = 0.809, P<0.01).

ACTH stimulation

Administration of ACTH induced a marked rise in cortisol concentration in both groups on Day 1. Cortisol concentrations were significantly higher 15 min after ACTH injection in foals of altrenogest treated mares (15.2, range 13.7–20.4 ng/ml) compared to control foals (7.6, range 4.7–11.3 ng/ml, P<0.05; Fig 3). Cortisol release in response to ACTH injection calculated as AUC was significantly more pronounced on Day 1 than on Day 5 in both groups (P<0.01, Wilcoxon test; Fig 3).

Plasma electrolytes

Immediately after delivery, potassium concentration in plasma of foals born to altrenogest-treated mares was significantly lower (3.8, range 3.8–3.9 mmol/l) than in control foals (4.1, range 3.9–4.1 mmol/l, P<0.05). Three hours after birth, plasma ionised calcium concentrations were significantly lower in foals of altrenogest-treated mares (1.38, range 1.37–1.44 mmol/l) compared to foals of the control group (1.50, range 1.47–1.53 mmol/l, P = 0.01). There was no difference in sodium or chloride concentrations between the groups during the first 48 h *post partum* (Table 2).

Discussion

Foals born to altrenogest-treated mares showed a lower N/L ratio on the first day *post partum* compared to control foals. The N/L ratio of healthy, mature foals at birth should exceed 2.5 and continue to rise within 24 h (Jeffcott *et al*. 1982). Foals of altrenogest-treated mares showed N/L ratios <2.5 on the first 2 days indicating prematurity (Jeffcott *et al*. 1982). This might, in part, be due to the fact that gestation on average was 8 days shorter in altrenogest-treated than in control mares, implying that altrenogest may advance parturition (Neuhauser *et al*. 2008) irrespective of fetal maturity. Interestingly, Alm *et al*. (1975) reported that treatment with progesterone also shortens gestation in mares, in this case resulting in the birth of live and healthy foals. However, in our study on the second day *post partum,* there was a rise in N/L ratio above 2 indicating a favourable prognosis for premature foals (Koterba 1990) and none of the foals born to altrenogest-treated mares showed adaptive problems after this time. Foals born to altrenogest-treated mares and control foals showed no differences in absolute leucocyte number, similar to results reported for mature mares treated with altrenogest for prolonged periods (Shideler *et al*. 1983).

In the present study, absolute cortisol values, although lower than described before, showed a typical increase after birth reaching maximal levels within 45 min and decreasing thereafter as reported in previous studies (Rossdale *et al*. 1973; Nathanielsz *et al*. 1975; Silver *et al*. 1991). Premature foals lack this characteristic increase and decrease (Nathanielsz *et al*. 1975), indicating that foals in our study were affected by altrenogest treatment to their dams but cannot be considered as immature. Interestingly, immediately after birth cortisol values were significantly higher in foals of altrenogest treated mares. Silver *et al*. (1984) reported an enhanced ACTH production at delivery due to the stress of birth. A prolonged second stage of labour (Neuhauser *et al*. 2008) may have caused more stress and subsequently higher cortisol concentrations in plasma immediately after parturition than in foals of nontreated mares.

Adrenocortical function is a suitable parameter to determine maturity of foals (Rossdale *et al*. 1973, 1982; Silver *et al*. 1984, 1991). Responsiveness of the adrenal gland to exogenous ACTH showed a maximum in term foals on the day of birth. Subsequently basal cortisol levels and the response of the adrenal to ACTH declined (Silver *et al*. 1984; Ousey *et al*. 2004). In premature foals, there was only a slight cortisol response to ACTH (Silver *et al*. 1984). In the present study, there was a marked cortisol release after administration of ACTH on the day of birth but there was only a small response in both groups on Day 5. This indicates that a stress hyporesponsive period, as demonstrated during Days 4–14 in neonatal rats (Vazquez and Levine 2005), may exist also in the foal. In the rat, it has been suggested that such a transient dampening of the hypothalamo-pituitary axis might protect the developing brain from glucocorticoid surges (Sapolsky and Meaney 1986; Dent *et al*. 2007). In contrast to the results in foals, in calves an increase in adrenal responsiveness to ACTH was found between Days 1 and 6 *post partum* (Steffen *et al*. 1990).

In the present study, only on Day 1 at 15 min after ACTH injection were cortisol levels higher in foals from altrenogest-

TABLE 2: Electrolyte concentration (mmol/l) in venous blood of foals born to altrenogest-treated mares and control foals during the first days *post partum* (altrenogest: n = 5 until 30 min and n = 4 thereafter, control: n = 7; data not shown for all time points)

	Sodium		Potassium		Chloride		Calcium	
Time	Altrenogest	Control	Altrenogest	Control	Altrenogest	Control	Altrenogest	Control
Birth	136 (135–137)	138 (136–139)	3.8 (3.5–3.8)[a]	4.1 (3.9–4.1)[a]	99 (99–101)	102 (99–104)	1.69 (1.62–1.82)	1.73 (1.71–1.78)
15 min	137 (136–139)	138 (136–139)	3.7 (3.4–4.2)	4.0 (3.9–4.2)	100 (100–104)	103 (101–104)	1.65 (1.58–1.70)	1.68 (1.60–1.72)
30 min	138 (137–139)	137 (134–138)	3.7 (3.7–4.3)	3.9 (3.6–4.1)	102 (102–105)	104 (101–106)	1.55 (1.46–1.65)	1.54 (1.47–1.63)
45 min	138 (136–139)	138 (135–140)	3.8 (3.8–4.0)	4.1 (3.7–4.1)	103 (101–104)	103 (101–105)	1.43 (1.36–1.53)	1.52 (1.44–1.56)
60 min	137 (135–138)	138 (134–138)	3.7 (3.7–3.7)	3.9 (3.7–4.1)	101 (100–104)	102 (100–103)	1.41 (1.33–1.49)	1.49 (1.41–1.57)
3 h	136 (136–138)	137 (134–138)	3.4 (3.1–3.7)	3.6 (3.6–4.0)	103 (101–105)	103 (100–104)	1.38 (1.33–1.44)[b]	1.50 (1.47–1.53)[b]
6 h	138 (134–138)	137 (136–137)	3.3 (3.0–3.7)	3.7 (3.3–3.8)	104 (99–104)	103 (102–104)	1.43 (1.41–1.50)	1.48 (1.47–1.53)
9 h	136 (135–137)	137 (135–137)	3.3 (3.0–4.0)	3.4 (3.1–3.7)	102 (100–103)	101 (101–104)	1.45 (1.38–1.48)	1.48 (1.47–1.50)
12 h	135 (133–136)	137 (136–138)	3.4 (3.0–4.0)	3.5 (3.1–3.7)	100 (99–103)	102 (99–104)	1.49 (1.39–1.58)	1.48 (1.46–1.53)
24 h	135 (131–138)	135 (133–137)	3.2 (2.9–4.0)	3.8 (3.3–4.0)	100 (100–104)	101 (99–101)	1.38 (1.34–1.51)	1.48 (1.41–1.54)
36 h	134 (132–137)	135 (134–137)	3.7 (3.2–4.6)	3.9 (3.8–4.3)	102 (101–103)	99 (99–104)	1.43 (1.39–1.50)	1.50 (1.46–1.53)
48 h	137 (133–138)	135 (134–137)	3.7 (3.2–4.2)	3.9 (3.7–4.2)	102 (101–103)	102 (98–103)	1.52 (1.40–1.56)	1.49 (1.43–1.55)

a: P<0.05; b: P = 0.01

treated mares than in control foals. Therefore, altrenogest treatment of late-pregnant mares neither influences adrenocortical maturation nor impairs cortisol release in the fetus to a major extent.

On the day of birth, a parallel increase in the N/L ratio and adrenocortical activity was not found, as reported in foals with increasing gestational age (Rossdale *et al*. 1982). High basal cortisol levels in plasma and a nonimpaired adrenal response to ACTH stimulation disagree with the findings of a low N/L ratio. Plasma cortisol concentrations in the horse fetus correlate well with tissue maturation (Fowden and Silver 1994; Fowden 1995). Although the low N/L ratio on the day of birth could be indicative for prematurity, it might also be due to an immunomodulatory effect of altrenogest. Progesterone receptors have been identified on rat leucocytes (Butts *et al*. 2007) and immunosuppressive effects of progesterone have been suggested (Szekeres-Bartho *et al*. 2005). On Day 2 after birth, N/L ratio and plasma cortisol levels were positively correlated, indicating that a gestagen-induced immunomodulation may have waned by this time. Additionally, a stimulatory effect of ACTH given on Day 1 cannot be excluded.

The finding that the N/L ration was lower in newborn foals from altrenogest-treated mares and at the same time foals were showing adaptive problems (Neuhauser *et al*. 2008), even though their hypothalamo-pituitary-adrenal axis appeared to be mature, suggests that the N/L ratio does not always reflect pituitary and adrenal maturity but can still be used successfully for identifying problem foals which require special care.

In the foals of the present study, potassium levels were lower only at birth, but sodium values were not influenced. Therefore, electrolyte disturbances due to renal or adrenal dysfunction are doubtful. During pregnancy, the placenta is primarily responsible for fluid and electrolyte homeostasis (Koterba *et al*. 1985) and altrenogest treatment cannot be excluded as an influence on placental electrolyte transfer. High progesterone levels during pregnancy have been reported to cause sodium retention and potassium loss (Shaftoe 1990) and, therefore, such effects might be augmented by exogenous altrenogest. In contrast, progesterone has antimineralocorticoid activities that have to be protected by extra-adrenal downstream conversion of progesterone (Quinkler *et al*. 2003).

Adrenal aldosterone secretion is regulated by the release of renin from the kidney (Greco and Stabenfeldt 1997) but can be also stimulated by ACTH (Arvat *et al*. 2000), which is elevated during parturtition (Silver *et al*. 1984). Aldosterone causes the redistribution of potassium from extracellular to intracellular compartments and augments renal potassium elimination (Verlander 1997). However, ACTH-induced aldosterone release does not explain lower potassium levels in foals born to altrenogest-treated mares.

Calcium transport to the fetus, via the placenta, is stimulated by parathyroid hormone-related protein, the fetal equivalent of parathyroid hormone (PTH) (Kruse 1992; Care 1997). At birth, supply of calcium to the fetus stops abruptly, leading to a decrease in fetal serum calcium concentrations. Low serum calcium levels activate PTH production, which is important for regulation of calcium homeostasis in post natal life (Bass and Chan 2006). These mechanisms might be impaired in foals of altrenogest-treated mares, causing slightly lower calcium concentrations 3 h after birth. Comparably, hypocalcaemia in premature infants resulting from immature parathyroid glands has been reported (Tsang *et al*. 1973). Calcium content in mares' mammary secretions increases before foaling (Leadon *et al*. 1984). Although electrolytes were not measured in mare's mammary secretions, it can also not be excluded that lower calcium concentration in foals born to altrenogest-treated mares might be caused by a slightly shorter gestation.

The results of the present study confirm that mares can deliver in the presence of elevated gestagen concentrations in plasma. High gestagen concentrations can block metabolism of pregnenolone via inhibition of 3β-hydroxysteroid dehydrogenase (Chavatte *et al*. 1997) and, therefore, altrenogest may reduce endogenous gestagen synthesis leading to the onset of parturition. However, in another study, altrenogest given to late-pregnant mares increased concentrations of the progesterone metabolite 5α-pregnane-3, 20-dione in plasma (Ousey *et al*. 2002). The mechanisms by which gestagens control myometrial function in the period immediately preceding parturition require further studies.

In conclusion, altrenogest treatment of pregnant mares until foaling did not have major effects on adrenocortical function in their foals. A reduced neutrophil/lymphocyte ratio in these foals suggests immunomodulatory effects of altrenogest on the fetus *in utero* and less dysmaturity of the foals. Serum electrolytes in newborn foals, with the exception of potassium immediately and calcium 3 h after birth, were not influenced by altrenogest treatment of mares.

Manufacturers' addresses

[1]Intervet, Vienna, Austria.
[2]Mila International, Florence, Kentucky, USA.
[3]Greiner, Kremsmünster, Austria.
[4]Hettich Zentrifugen, Tuttlingen, Germany.
[5]Siemens, Vienna, Austria.
[6]Radiometer, Copenhagen, Denmark.
[7]Novartis, Nürnberg, Germany.
[8]SPSS, Chicago, Illinois, USA.

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