



ELSEVIER

Theriogenology 58 (2002) 887–898

Theriogenology

Aberrations in uterine contractile patterns in mares with delayed uterine clearance after administration of detomidine and oxytocin

Marcela von Reitzenstein^a, Megan A. Callahan^a,
Peter J. Hansen^b, Michelle M. LeBlanc^{a,*}

^aDepartment of Large Animal Clinical Sciences, University of Florida, Gainesville, FL 32610-0136, USA

^bDepartment of Animal Sciences, University of Florida, Gainesville, FL 32610-0136, USA

Received 11 July 2001; accepted 31 August 2001

Abstract

An experiment was conducted to determine whether the uterotonic effects of oxytocin, a drug used to treat mares that have a delay in uterine clearance were affected by the sedative detomidine (an α_2 -agonist), a drug used to treat fractious mares. An additional objective was to identify propagation patterns of uterine contractions and determine whether these patterns differed between normal mares and mares with delayed uterine clearance (DUC). Intrauterine pressure was measured in five reproductively normal mares and four mares with DUC during estrus using an 8-F Milar catheter with two discrete pressure sensors. Mares received one of three treatments in random order: detomidine (0.001 mg/kg; i.v.); detomidine followed in 10 min by oxytocin (10 IU; i.v.); and saline (0.9% NaCl 0.5 ml; i.v.) followed in 10 min by oxytocin. All treatments induced waves of contractions; however, only three mares with DUC exhibited contractions after administration of detomidine. Normal mares experienced more uterine contractions ($P < 0.01$) that tended to last longer ($P < 0.06$), and were of greater intensity ($P < 0.04$) than mares with delayed clearance. Administration of detomidine before oxytocin increased the number of contractions ($P < 0.02$) and increased the maximum intrauterine pressure in the uterine horn ($P < 0.05$) in normal mares as compared to response after administration of saline and oxytocin. Detomidine had no effect in mares with delayed clearance. All mares had more propagating than non-propagating uterine contractions (74 ± 8 versus $25 \pm 8\%$, respectively). Normal mares exhibited a normal propagation pattern more frequently ($P < 0.0001$) than mares with DUC. Simultaneous ($P < 0.05$) and inverted ($P < 0.03$) contractions occurred more frequently in mares with DUC. Administration of detomidine increased the number ($P < 0.01$), and tended to increase the percentage ($P < 0.07$) of normal propagating uterine contractions in normal mares, but did not affect propagation patterns in mares with DUC. In conclusion, detomidine augmented the uterotonic effect of oxytocin in normal mares but not in mares

* Corresponding author. Tel.: +1-859-233-0371; fax: +1-859-255-5367.

E-mail address: leblancm@mail.vetmed.ufl.edu (M.M. LeBlanc).

with DUC. Data suggest that mares with DUC have a defect in myoelectrical signaling and a decrease in the contractile strength of the uterine muscle.

© 2002 Elsevier Science Inc. All rights reserved.

Keywords: Mare; Intra-uterine pressure; Propagation; Detomidine; Oxytocin

1. Introduction

Some mares experience a delay in evacuation of uterine contents after breeding, leading to increased susceptibility to persistent endometritis [1–4]. Delayed uterine clearance (DUC) is associated with diminished intensity and frequency of uterine contractions [5]. While the specific mechanisms responsible for diminished myometrial contractility are not known, an *in vitro* study showed that uterine muscle collected from mares that experienced DUC exhibits an intrinsic contractile dysfunction [6]. A defect in neuronal signaling may also contribute to the aberration in uterine contractility in mares with DUC.

Xylazine is an α -adrenergic receptor agonist with both α_1 and α_2 effects that is commonly used to sedate horses and which causes a tetanic increase in intrauterine pressure when administered during estrus [7,8]. If xylazine was given before oxytocin, the duration of uterine contractions was increased in mares with DUC compared to reproductively normal mares [7]. In the same study, administration of acepromazine, a predominantly α_1 -antagonist, decreased the number of contractions in mares with DUC but had no effect on the oxytocin induced contraction pattern in normal mares. We speculate that the enhanced response to α -agonists and antagonists observed in mares with DUC when sedatives are administered before oxytocin may be due to denervation supersensitivity. It is not known if these effects are mediated through α_1 or α_2 receptors, or indeed which type of adrenergic receptor predominates in the equine uterus. Detomidine, another commonly used α_2 -agonist in the horse [9] has a more potent α_2 effect and minimal α_1 effect as compared to xylazine [8]. Evaluation of effects of detomidine in mares with DUC will clarify whether the effect of xylazine on intrauterine pressure is due to its α_1 or α_2 properties, and possibly identify what is the neuronal defect.

A myometrial defect may present itself as an alteration in the frequency, duration, or intensity of contractions or in the pattern of propagation. Propagation and intensity of uterine contractions have been studied in women, rats and mice in relation to dystocia [10–13]. Propagation is the spreading or dissemination of a contraction of an individual smooth muscle throughout the myometrium [11] and is caused by action potentials triggered in pacemaker regions [5]. Propagation of a contraction normally originates in the uterine horn near the end of the uterine tube [11–13]. It then spreads from the pacemaker area throughout the uterus [11]. An inverted propagation pattern has been described in women experiencing difficult delivery. Inverted contractile waves begin in the lower part of the uterus and spread upward towards the fundus [11]. The pattern of propagation and the intensity of uterine contractions may be important for proper emptying of uterine content, especially in pluriparous mares whose uterine body is located ventral to the pelvis.

The objective of this study was to determine the uterine contractile responses of mares with DUC after administration of detomidine and oxytocin, and to determine if the response differs from that of reproductively normal mares.

2. Materials and methods

2.1. Animals

Five reproductively normal mares and four mares diagnosed as having DUC were used. The mares were housed on pasture and fed a 10% protein grain concentrate twice daily and had free access to Coastal Bermuda hay. Mares classified as reproductively normal were free of uterine inflammation as defined by physical examination, uterine culture, cytology, and biopsy. Mares had biopsy scores of Grade 1 or 2a according to the system of Kenney [14]. Additionally, normal mares cleared more than 50% of a radioactive colloid as measured by scintigraphy within 2 h of its infusion into the uterus [15]. The mares were 8–15 years of age and either nulliparous or pluriparous. Mares classified as having a delay in uterine clearance were between 14 and 24 years old, were pluriparous and had histories of infertility. They cleared negligible amounts of radiocolloid from their uteri within 2 h of infusion and had a Grade 2b or 3 endometrial biopsy score due to inflammation, lymphatic lacunae or periglandular fibrosis. Mares were teased daily by a stallion to determine the onset of behavioral estrus. Once in estrus, the reproductive tract was examined daily by palpation per rectum and transrectal ultrasonography. Experiments were conducted when the mare had a dominant follicle that was at least 35 mm in diameter.

2.2. Study design and collection of data

Each mare received one of three treatments in random order during estrus, prior to ovulation. Treatments were administered over 3 days. There was a minimum of 20 h between treatments to avoid possible residual effects of a drug on intrauterine pressure. Two of the nine mares received treatments in more than one estrous cycle. Treatment 1 consisted of administration of detomidine (Dormosedan[®] Pfizer Animal Health, West Chester, PA) intravenously (0.001 mg/kg), Treatment 2 consisted of administration of detomidine 10 min before administration of oxytocin (Oxytocin injection[®], The Butler Company, Columbus, OH; 10 IU; i.v.), and Treatment 3 consisted of administration of saline (0.9% physiologic salt NaCl solution[®], USP, Baxter Health Care Corp. Deerfield, IL; 0.5 ml, i.v.) 10 min before administration of oxytocin. Intrauterine pressure was measured as follows: baseline intrauterine pressure was recorded for 10 min before drug administration in each mare. In Treatment 1, intrauterine pressure was recorded for 60 min after administration of detomidine. In Treatments 2 and 3, intrauterine pressure was recorded for 10 min after administration of detomidine or saline, and then for an additional 60 min after oxytocin was given.

Intrauterine pressure was measured with a Millar probe 8-F catheter (Millar Instruments, Inc. Houston, TX). Prior to its insertion into the uterus per vaginum, the tail of each mare was wrapped, pulled to the side and the perineum washed thoroughly. The probe had two pressure sensors located 5 cm apart beginning at the tip. The probe was placed such that the first sensor was located in one of the uterine horns and the second in the uterine body (Fig. 1B). The position of the catheter was verified by transrectal ultrasonography and then secured in place by suturing it to the vulva. A physiograph (Sensor Medics Corp., Yorba Linda, CA) was connected to the pressure probe for direct analogue recording. The channel

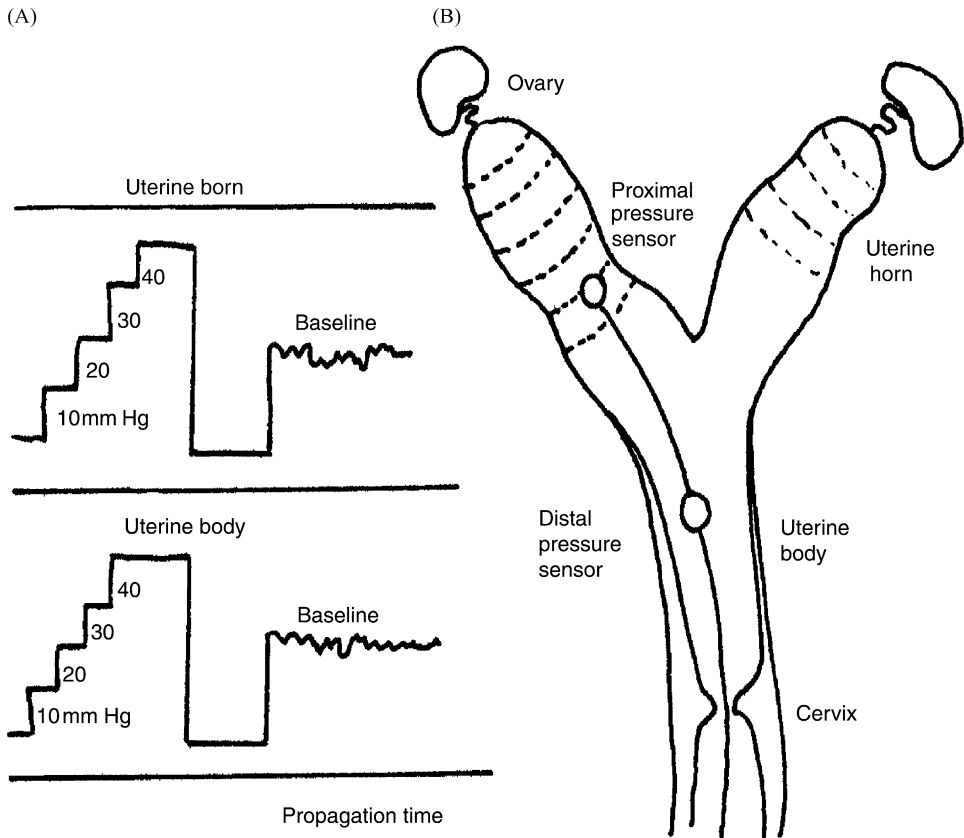


Fig. 1. (A) Calibration method used to measure intensity of uterine contractions. The probe was calibrated by placing it into a sealed tube connected to a manometer. Pressure sensors in the probe produced an electrical output signal, which varied in direct proportion to the applied pressure. (B) Location of the pressure sensors in the uterus.

sensitivities ranged from 0.01 to 0.02 mV/mm. The pressure sensors on the probe were calibrated with a mercury manometer before each study in order to measure the amplitude of uterine contractions. (Fig. 1A; the pressure sensors produce an electrical output signal, which varies in direct proportion to the applied pressure). The probe was calibrated by placing the end with the pressure sensors into a sealed tube (filled with air using a manual pump) and connecting the opposite end to the physiograph. The air in the sealed tube was increased so that the pressures recorded by the pressure sensors equaled 10, 20, 30, and 40 mmHg. Deflections from baseline for the four pressure readings were marked with the physiograph recording-chart pen on the physiograph paper. The outgoing signal from the physiograph was also digitized and stored in a computer.

The signals were sampled at a 50 Hz acquisition rate and stored by a commercial graphics package (CODAS; Dataq Instruments, Akron, OH). Any baseline deviation caused by urination, defecation, or excessive movement was recorded. At the conclusion

of a recording session, the position of the probe was verified by transrectal ultrasonography before it was removed.

Definitions of the variables measured were as follows: baseline was the median of all pressure deflections measured in the 10 min period prior to drug administration. Start time for a contraction was defined as the first second that intrauterine pressure exceeded 1.5 S.D. from the baseline; stop time was defined as the last second before intrauterine pressure returned to baseline. Duration of contractions was the number of minutes from the start of the first contraction to the end of the last contraction. Mean duration of a single contraction was the mean length, measured in minutes, of each uterine contraction. The time to onset of the first contraction was the number of minutes from drug administration to the start of the first contraction. Maximum intrauterine pressure was the highest deflection recorded, in mmHg, from the onset of the first contraction after drug administration until the end of the recordings. Time to maximum intrauterine pressure (mmHg) was the time in minutes from the onset of the first contraction to peak amplitude. Three patterns of propagation were recorded: normal propagation—the uterine horn contracted before the uterine body (Fig. 2A); simultaneous propagation—both horn and body contracted simultaneously (Fig. 2C); and inverted propagation—the uterine body contracted before the uterine horn (Fig. 2B). Propagation time was defined as the length of time for a contraction to

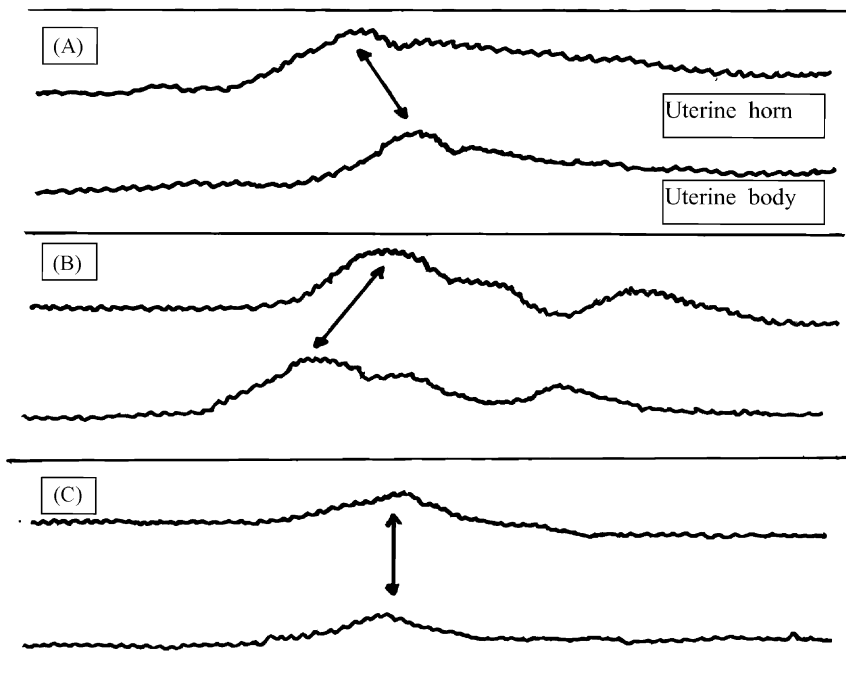


Fig. 2. Graphic depiction of propagation patterns. Panel A shows normal uterine propagation with contraction first occurring in the uterine horn and then in the uterine body. Panel B shows inverted uterine propagation with contraction first occurring in the uterine body and then in the uterine horn. Panel C shows simultaneous uterine contraction.

travel from one pressure sensor to the other. Propagation speed was calculated by dividing propagation time by the distance (50 mm) between the two pressure sensors.

2.3. Statistical analysis

Data were analyzed by least-squares analysis of variance using the General Linear Models Procedure of the Statistical Analysis System (SAS 1989). Independent variables were group (normal versus DUC), mare nested within group, region of the uterus (horn versus body), and treatment. Mare was considered a random effect and other main effects were considered fixed. Data were analyzed with a mathematical model considering all interactions; data were then reanalyzed after removal of non-significant interactions.

Differences between levels of treatment were determined in two ways. Orthogonal contrasts were performed to separate effect of treatment into two, single degree of freedom comparisons (Treatment 1 versus 2 and 3; Treatment 2 versus 3). In addition, the mean separation test, pdiff procedure from SAS (SAS 1989) was used to distinguish differences between least-squares means.

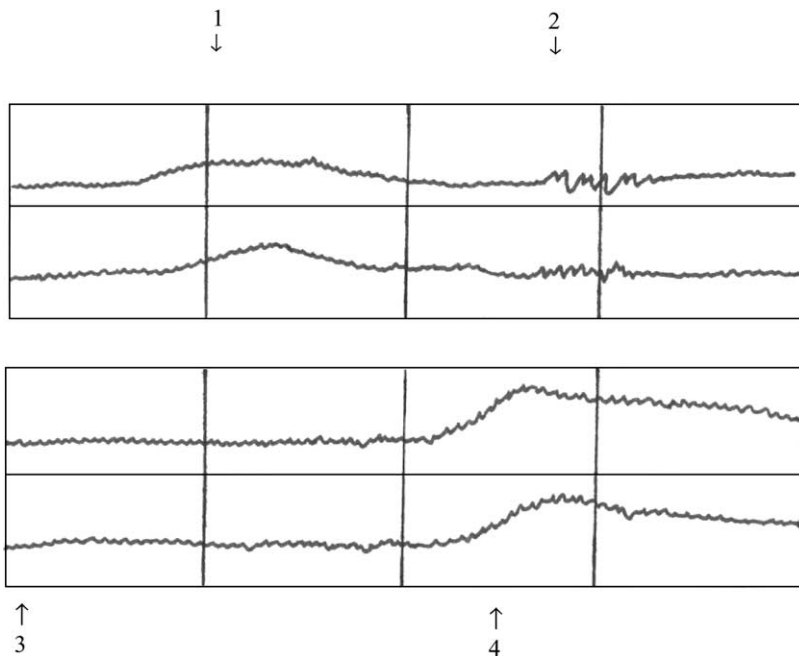


Fig. 3. Tracing of a typical uterine pressure recording taken from a reproductively normal mare. Each block represents 36 s of recording. First row of eight blocks depicts baseline recording. Second row of eight blocks depicts the effect of detomidine treatment on intrauterine pressure. Upper panel of four blocks represents intrauterine pressure from the horn, lower panel represents intrauterine pressure from the body. (1) Pretreatment spontaneous propagating uterine contraction. (2) Uterine contraction caused by movement, urination or defecation. (3) Injection of detomidine i.v. (4) First post-treatment uterine contraction.

3. Results

During baseline recordings or after saline injection, contractions were rare. A total of 15 isolated contractions that reached a maximum pressure of 5–10 mmHg; nine of them were propagating uterine contractions (Fig. 3). All treatments induced waves of uterine contractions but the characteristics of uterine contractions varied between groups (Table 1). In particular, normal mares experienced more uterine contractions ($P < 0.01$), their uterine contractions tended to last longer ($P < 0.06$) and were of greater intensity ($P < 0.04$) than those of mares with delayed clearance. The time to maximum intrauterine pressure was longer ($P < 0.05$) in normal mares than in mares with DUC.

Table 1

Number and duration of uterine contractions, time to onset of the first uterine contraction, time to the maximum intrauterine pressure, percentage of propagating uterine contractions and percentage of non-propagating uterine contractions (LSM \pm S.E.M.) in reproductively normal mares (Normal, $n = 5$) and mares with DUC ($n = 4$) in each treatment

| Group | Detomidine | Detomidine and oxytocin ¹ | Saline and oxytocin ¹ |
|--|-------------------------|--------------------------------------|----------------------------------|
| Number of contractions ² | | | |
| Normal | 6 \pm 2 ^a | 17 \pm 2 ^c | 11 \pm 2 ^a |
| DUC | 3 \pm 2 ^b | 6 \pm 2 ^{a,b} | 7 \pm 2 ^{a,b} |
| Duration of contractions (min) ³ | | | |
| Normal | 46 \pm 8 | 58 \pm 8 ^a | 45 \pm 8 |
| DUC | 28 \pm 9 ^b | 37 \pm 9 | 43 \pm 9 |
| Time to onset (min) ⁴ | | | |
| Normal | 8 \pm 5 | 1 \pm 2 ^a | 1 \pm 2 ^a |
| DUC | 14 \pm 6 ^b | 6 \pm 2 | 1 \pm 2 ^a |
| Time to maximum intrauterine pressure (min) ⁵ | | | |
| Normal | 25 \pm 5 ^b | 22 \pm 5 ^b | 17 \pm 5 |
| DUC | 8 \pm 5 ^a | 14 \pm 5 | 8 \pm 5 |
| Percentage of propagating contractions ⁶ | | | |
| Normal | 80 \pm 13 | 85 \pm 13 | 64 \pm 13 |
| DUC | 49 \pm 17 | 83 \pm 14 | 84 \pm 14 |

Note: There was no significant difference in any of the parameters shown in this table between uterine horn and body. The values shown are from recordings taken in the uterine horn. Numbers with different superscripts are significantly different ($P < 0.05$).

¹ Parameters measured after oxytocin administration.

² Number of contractions was affected by group ($P < 0.01$) and treatment ($P < 0.02$). Treatment by group interaction was bordering on significance ($P < 0.11$). Moreover, when analyzed within group, treatment affected number of contractions for normal mares ($P < 0.02$) but not for DUC mares. Using orthogonal contrast, detomidine differed from other treatments ($P < 0.01$ for the entire data and $P < 0.02$ for normal mares) and detomidine and oxytocin tended to differ from saline and oxytocin ($P < 0.09$ for the entire data and $P < 0.08$ for normal mares only).

³ Duration was affected by group ($P < 0.06$). Using orthogonal contrast, duration for detomidine and oxytocin was greater ($P < 0.01$) than for the other two treatments.

⁴ Time to onset was affected by group ($P < 0.02$).

⁵ Time to maximum intrauterine pressure tended to be affected by group ($P < 0.09$).

⁶ No effect of group or treatment.

Detomidine produced profound sedation in all mares. It induced waves of uterine contractions in all normal mares (Fig. 3) but in mares with DUC, detomidine induced uterine contractions only in two of the mares when it was injected alone and in three of the mares after it was injected before oxytocin. The number and intensity of contractions after administration of detomidine and oxytocin differed between normal mares and those with DUC. Detomidine augmented the effect of oxytocin in normal mares by increasing the number of contractions ($P < 0.02$) but it did not increase the number of contractions in mares with DUC. The effect of treatment on number of uterine contractions interacted with location in the uterus ($P < 0.05$; Table 2). In particular, the increase in number of contractions caused by detomidine and oxytocin was greater for the uterine horn than for the uterine body. Also, there was a three way interaction ($P < 0.05$) affecting maximum uterine pressure (Table 2).

In normal mares, the maximum uterine pressure was increased by detomidine and oxytocin relative to other treatments in the uterine horn, but not in the body. In mares with DUC, no treatment increased maximum uterine pressure at any location. Both groups exhibited more propagating uterine contractions than non-propagating contractions (Table 1). Mean propagation speed was 0.93 mm/s in reproductively normal mares and 1 mm/s in mares with DUC. Three types of propagating contractions were observed: normal, simultaneous and inverted. A greater proportion of contractions were classified as normal for reproductively normal mares than mares with DUC ($P < 0.0001$). In contrast,

Table 2

Interactions between pressure sensor location, group and treatment in regard to number of uterine contractions and maximum intrauterine pressure (mmHg; LSM \pm S.E.M.) in reproductively normal mares and mares with DUC

| Group | Treatment | Location in the uterus | Number of contractions ¹ | Maximum intrauterine pressure (mmHg) ² |
|--------|--------------------------------------|------------------------|-------------------------------------|---|
| Normal | Detomidine | Horn | 6 \pm 1 | 43 \pm 16 |
| | | Body | 6 \pm 1 | 28 \pm 16 |
| Normal | Detomidine and oxytocin ³ | Horn | 20 \pm 1 | 148 \pm 16 |
| | | Body | 14 \pm 1 | 31 \pm 16 |
| Normal | Saline and oxytocin ³ | Horn | 11 \pm 1 | 49 \pm 16 |
| | | Body | 11 \pm 1 | 35 \pm 16 |
| DUC | Detomidine | Horn | 3 \pm 1 | 30 \pm 17 |
| | | Body | 3 \pm 1 | 18 \pm 17 |
| DUC | Detomidine and oxytocin ³ | Horn | 8 \pm 1 | 8 \pm 17 |
| | | Body | 5 \pm 1 | 11 \pm 17 |
| DUC | Saline and oxytocin ³ | Horn | 7 \pm 1 | 8 \pm 17 |
| | | Body | 7 \pm 1 | 16 \pm 17 |

¹ Number of contractions was affected by group ($P < 0.01$) and treatment ($P < 0.02$), location in the uterus ($P < 0.1$) and treatment by uterine location ($P < 0.05$).

² Maximum intrauterine pressure was affected by group ($P < 0.04$), location in the uterus ($P < 0.03$), group by uterine location ($P < 0.03$), treatment by uterine location ($P < 0.08$), and group by treatment by uterine location ($P < 0.05$).

³ Contractions and intensity of contraction were measured after oxytocin administration.

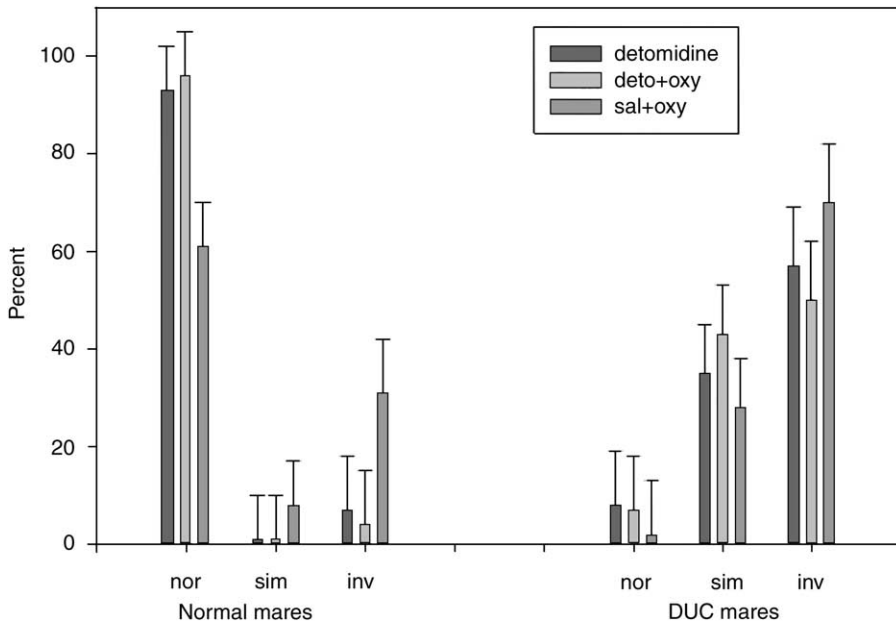


Fig. 4. Percentage of uterine contractions that exhibit a normal (nor), simultaneous (sim), or inverted (inv) propagation pattern in reproductively normal mares (Normal; $n = 5$) and mares with DUC ($n = 4$). Data are LSM \pm S.E.M. Treatment affected the percentage of normal ($P < 0.0001$), simultaneous ($P < 0.05$) and inverted ($P < 0.03$) propagating uterine contractions.

reproductively normal mares had a smaller proportion of simultaneous ($P < 0.05$), and inverted ($P < 0.03$) contractions, than mares with DUC (Fig. 4). In normal mares, administration of detomidine before oxytocin increased the percentage of the number of normal propagating contractions classified as normal compared to saline and oxytocin ($P < 0.01$; Fig. 4). Treatment did not affect the percentage of propagation patterns in mares with DUC.

4. Discussion

The uterus is richly innervated with adrenergic receptors [16], and α_2 -agonists such as xylazine or detomidine appear to interact with these receptors in uterine smooth muscle to cause an increase in intrauterine pressure. De Lille et al. [7] showed that xylazine caused a tetanic uterine contraction for 11 min when administered to normal or infertile mares in estrus. In this study, detomidine caused waves of contractions in all reproductively normal mares but in only two of four mares with DUC when it was injected alone and in three of the four mares when it was injected before oxytocin. Differences in the contraction pattern induced by the two drugs may be due to differences in the specificity for α -adrenoreceptors. Detomidine has a greater affinity for α_2 receptors than xylazine does. Detomidine binds to α_2 receptors 260 times more frequent than it does to α_1 receptors, while xylazine binds α_2

receptors only 160 times more often than it does to α_1 [8]. The tetanic contraction observed after xylazine administration may be due to the drug binding to α_1 receptors and not α_2 receptors.

Detomidine did not consistently induce uterine contractions nor did it augment the response to oxytocin in mares with DUC. These findings may be due to decreased α -adrenergic receptors, unresponsiveness of receptors, or due to a defect in myometrial signaling in mares with a delay in uterine clearance. In other species, repeated stretching of the uterus from numerous pregnancies adversely affects terminal nerve endings to change the ratio of receptor types or numbers [16]. Mares with DUC used in this study were pluriparous and therefore had experienced repeated uterine stretching. Degenerative uterine changes including fibrosis, chronic inflammation and angiogenesis may also interfere with the uterine contractile response of these mares.

The maximum intrauterine pressure attained after treatment differed between groups. Reproductively normal mares responded to each treatment by exhibiting an increase in intrauterine pressure in the horns. In contrast, mares with DUC showed no increase in intrauterine pressure. Recent work indicates that mares with DUC have an intrinsic contractile defect of the myometrium. Experiments to study myometrial contractility in vitro showed that the tension produced in uterine myometrium from mares with DUC in response to oxytocin was less than for myometrium from older, normal mares [6]. This study agrees with that report. The number of uterine contractions and maximum intrauterine pressure were lower after all three treatments in mares with DUC compared to reproductively normal mares. The greatest increase in intrauterine pressure was seen in the uterine horns of reproductively normal mares after administration of detomidine and oxytocin. It is not known why administration of an α_2 -agonist increases the response to oxytocin. Perhaps detomidine stimulates neurons that promote myometrial responsiveness to oxytocin; another mechanism may be signaling pathways activated in the myometrium by detomidine potentiate oxytocin induced signal transduction.

This is the first report that identified differences in propagation patterns of uterine contractions in the mare. Reproductively normal mares most frequently exhibited a normal propagation pattern, while mares with DUC exhibited an inverted propagation pattern and simultaneous uterine contraction most frequently after treatment. The number of uterine contractions and the percentage of contractions classified as a normal propagation pattern were increased in reproductively normal mares after administration of detomidine and oxytocin. This effect was not observed in mares with DUC. In the only other report on propagation in the mare [17] no statistical difference in the frequency of propagation patterns was observed between the two groups of mares after they received oxytocin. Differences between the two studies may be related to differences in experimental design, methodology and statistical analysis. Uterine contractions were defined in the earlier study by Cadario et al. [17] as any positive deflection that exceeded 2.5 times the height of baseline. In this study, contractions were defined as positive deflections greater than 1.5 times above baseline deflections. Data were interpreted manually from physiograph chart recordings in the former study. In this study, data were collected into a computer with digitalized storing system and analyzed with a sophisticated graphics software program.

Abnormal propagation patterns have been reported in women. Women who experience normal labor have contractile waves originating between the upper uterine segment and

one of the fallopian tubes. The contractions are propagated coordinately and in a decreasing gradient from the upper to the lower segment of the uterus [11]. Oxytocin augmentation does not change this pattern. In contrast, women who require a cesarean section because of ineffective labor have reverse gradient of uterine activity. The lower segment (2–4 in. cranial to the cervix) contracts more strongly than the upper uterine segment both before and after oxytocin administration [18].

Uterine contractile activity is a consequence of depolarization and repolarization of the plasma membrane of smooth muscle cells [19]. It has been hypothesized that bundles of smooth muscle cells act as specialized pacemaker cells and initiate uterine activity [20,21]. However, unlike the heart, pacemakers in the uterus are not represented by a discrete anatomical location. Any myometrial cell in the uterus may be capable of assuming the function of a pacemaker cell, and pacemaker regions may shift from one site to another [20]. Our data suggest that there is a pacemaker region in the myometrium of the uterine horns in normal mares, causing the initial contraction to originate in the horn and propagate towards the cervix. In contrast, the pacemaker region in mares with DUC appears more frequently to be in the uterine body. The location of the pacemaker in the uterine body may be intrinsic to mares with DUC, or may be developed as a consequence of stretching and hypertrophy from repeated pregnancies. Smooth muscle cells may develop a longer resting membrane potential than neighboring cells making them hyper-excitabile and essentially ectopic pacemaker cells [20].

In conclusion, detomidine and oxytocin induced waves of contractions that were propagated from the uterine horn to body in reproductively normal mares. Detomidine augmented the uterine response to oxytocin in these mares by increasing uterine contractions and pressure. Mares with DUC had altered patterns of propagation of uterine contractions, reduced number and strength of uterine contractile responses, and responded aberrantly to detomidine. These findings suggest that mares have an intrinsic contractile defect of the myometrium and possibly a defect in myoelectrical signaling.

Acknowledgements

Project supported by the Dorothy Havemeyer Foundation. The authors thank Drs. A. Merrit, M. Cadario and F. Freytes and Mr. J. Burrow and E. Reller for technical assistance.

References

- [1] LeBlanc MM, Asbury AC, Lyle SK. Uterine clearance mechanisms during the early post-ovulatory period in mares. *Am J Vet Res* 1989;50:864–7.
- [2] Pycocock JF, Allen WE. Pre-chemotactic and chemotactic properties of uterine fluid from mares with experimentally induced endometritis. *Vet Rec* 1988;123:193–5.
- [3] Pycocock JF, Newcombe JR. Assessment of the effect of three treatments to remove intrauterine fluid on pregnancy rate in the mare. *Vet Rec* 1996;138:320–3.
- [4] Troeddsen MHT, Liu IKM. Uterine clearance of non-antigenic markers (^{51}Cr) in response to a bacterial challenge in mares potentially susceptible and resistant to chronic uterine infections. *J Reprod Fertil Suppl* 1991;44:283–8.
- [5] Wray S. Uterine contraction and physiological mechanisms of modulation. *Am J Physiol* 1993;264:C1–C18.

- [6] Rigby S, Varner D, Blanchart T, Colleran P, Wilkerson K, Delp M, et al. Intracellular Ca^{2+} and in vitro myometrial contractility of uterine muscle from mares susceptible to endometritis. In: Proceedings of the Annual Conference on Society of Theriogenology, 1999. p. 34 [abstract].
- [7] De Lille A, Silvers ML, Cadario ME, Tran TQ, Cage CL, LeBlanc MM. Interactions of xylazine, acepromazine with oxytocin and the effects of these interactions on intrauterine pressure in normal mares and mares with delayed uterine clearance. *J Reprod Fertil Suppl* 2000;56:373–9.
- [8] Muir WW, Hubbell JAF, Skarda RT, Bednarski RM. Xylazine, detomidine, medetomidine. In: Handbook of veterinary anesthesia. 2nd ed. St. Louis: Mosby, 1995. p. 30–1.
- [9] Hamm D, Turchi P, Jochle W. Sedative and analgesic effects of detomidine and romifidine in horses. *Vet Rec* 1995;136:324–7.
- [10] Andersen HF, Barclay ML. A computer model of uterine contractions based on discrete contractile elements. *Obstet Gynecol* 1995;86:108–11.
- [11] Caldeyro-Barcia R, Poseiro JJ. Physiology of the uterine contraction. *Clin Obstet Gynecol* 1960;3:236–41.
- [12] Lammers WJEP, Stephen B, Hamid R, Harron DWG. The effects of oxytocin on the pattern of electrical propagation in the isolated pregnant uterus of the rat. *Pfluegers Arch Eur J Physiol* 1999;437:363–70.
- [13] Reynolds SRM, Hellman LM, Bruns P. Patterns of uterine contractility in women during pregnancy. *Obstet Gynecol Surv* 1948;3:629–46.
- [14] Kenney RM. Cyclic and pathologic changes of the mare endometrium as detected by biopsy, with a note on early embryonic death. *J Am Vet Med Assoc* 1978;172:241–62.
- [15] LeBlanc MM, Neuwith LA, Asbury AC, Tran T, Mauragis D, Klapstein E. Scintigraphic measurement of uterine clearance in normal mares and mares with recurrent endometritis. *Equine Vet J* 1994;26:293–8.
- [16] Guyton AC, Hall JE. The autonomic nervous system the adrenal medulla. In: Textbook of medical physiology. 9th ed. Philadelphia: Saunders, 1996. p. 774–8.
- [17] Cadario ME, Merritt AM, Archbald LF, Thatcher WW, LeBlanc MM. Changes in intrauterine pressure after oxytocin administration in reproductively normal mares and in those with a delay in uterine clearance. *Theriogenology* 1999;51:1017–25.
- [18] Margono F, Minkoff H, Chan E. Intrauterine pressure wave characteristics of the upper and lower uterine segments in parturients with active-phase arrest. *Obstet Gynecol* 1948;81(4):481–5.
- [19] Riemer RK, Heymann MA. Regulation of uterine smooth muscle function during gestation. *Pediatr Res* 1998;44:1–24.
- [20] Jain V, Sade GR, Garfield RE. Uterine contraction. In: Encyclopedia of reproduction, vol. 4. San Diego, CA: Academic Press, 1999. p. 932–41.
- [21] Parkington HC, Harding R, Sigger JN. Coordination of electrical activity in the myometrium of pregnant ewes. *J Reprod Fertil* 1988;82:697–705.